preparing a transgenic *Caenorhabditis elegans* nematode that expresses a detectable marker linked to *LOV-1* protein;

mutagenizing the nematode;

selecting nematodes or offspring thereof that have altered patterns of expression of *LOV-1*; and

identifying the gene responsible for the alteration.

77. (Amended twice) A method for identifying transcriptional regulators of *lov-1*, comprising:

preparing a transgenic *Caenorhabditis elegans* nematode that expresses a detectable marker linked to *LOV-1* protein;

mutagenizing the nematode; and

selecting nematodes or offspring thereof that have altered levels of expression of the protein.

REMARKS

Any fees that may be due in connection with this paper or this application may be charged to Deposit Account No. 50-1213. If a Petition for extension of time is needed, this paper is to be considered such Petition.

Claims 1, 5, 9-11, 15-17, 21, 22, 25-32, 42, 49, 74-77 and 82-84 are presently pending in this application. Claims 88 and 89, which are directed to subject matter that is withdrawn from consideration as being drawn to non-elected subject matter, are cancelled without prejudice or disclaimer. Applicant reserves the right to file divisional applications to the non-elected subject matter and continuations to any cancelled subject matter.

Claims 9, 27, 29 and 42 are amended to more particularly point out the subject matter of the claims as required by the Examiner and to place the claims and dependents thereof in condition for allowance. Claims 28, 31, 32, 76 and 77 are amended for typographical and grammatical inconsistencies and errors.

None of the amendments to the claims have been made in order to overcome art of record.

Claims 21-22, 25-26 and 49 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. Applicant respectfully submits that in light of the traversal of the rejection of base claim 1 and dependents thereon, claim 1 and, hence all claims dependent thereon, including claims 21-22, 25-26 and 49 should be in condition for allowance.

A marked up copy per 37 C.F.R. §1.121 of the amended claims is attached to this response.

THE REJECTION OF CLAIMS 27-32, 42, 74-77 and 82-84 UNDER 35 U.S.C. § 112, FIRST PARAGRAPH

Claims 27-32, 42, 74-77 and 82-84 are rejected under 35 U.S.C. §112, first paragraph, because the specification, while concededly being enabling for a mutant *C. Elegans* that comprises a mutant *lov-1* gene exhibiting a phenotype of defective mating behavior particularly in the male sensory behaviors response and location of vulva, allegedly does not reasonably provide enablement for transgenic *Caenorhabditis* nematodes comprising a vector encoding the nucleic acid sequence set forth in SEQ ID NO. 3, or any nucleic acid that encodes a mutated LOV-1 protein. The Examiner is not persuaded by Applicant's arguments filed responsive to the Office Action of November 8, 2000, in which Applicant asserted that it would not require undue experimentation to introduce the *C. elegans lov-1* gene into a nematode of another *Caenorhabditis* species, and that those of skill in the art knew and recognized the relatedness among species of the genus *Caenorhabditis*.

The Examiner further alleges that while the specification describes the production of *C. elegans* that have been mutagenized and screened for a phenotype of interest there are allegedly has no working examples in the

specification that correlate introduction and expression of a *lov-1* transgene into a *Caenorhabditis* and a corresponding phenotype that results from transgene expression. Furthermore, the Examiner alleges that the specification provides no working examples that demonstrate identification of genes and regulatory factors involved in polycystic kidney disease using mutagenized *C. elegans*, nor does it show a correlation between a nucleic acid isolated by the same method and polycystic kidney disease.

As discussed below, in the interest of advancing claims to allowance, the rejection on the basis of scope of enablement of any and all transgenic *Caenorhabditis* species is obviated by amendment of claims 27-32 and 42 to recite "*C. Elegans*". The rejection based on lack of enablement of (a) the production of a transgenic *Caenorhabditis* species; and (b) the identification of genes and regulatory factors involved in polycystic kidney disease and a correlation between the nucleic acids isolated by the same method and polycystic kidney disease, is respectfully traversed.

Relevant law

To satisfy the enablement requirement of 35 U.S.C § 112, first paragraph, the specification must teach one of skill in the art to make and use the invention without undue experimentation. Atlas Powder Co. v. E.I. DuPont de Nemours, 750 F.2d 1569, 224 USPQ 409 (1984). This requirement can be met by providing sufficient disclosure, either through illustrative examples or terminology, to teach one of skill in the art how to make and how to use the claimed subject matter without undue experimentation. This clause does not require "a specific example of everything *within the scope* of a broad claim." In re Anderson, 176 USPQ 331, at 333 (CCPA 1973), emphasis in original. Rather, the requirements of § 112, first paragraph "can be fulfilled by the use of illustrative examples **or** by broad terminology." In re Marzocci et al., 469 USPQ 367 (CCPA 1971) (emphasis added).

Scope of enablement rejection with respect to the production of any and all transgenic *Caenorhabditis* species

The Examiner has considered Applicant's arguments filed responsive to the Office Action of November 8, 2000, in which Applicant asserted that the references cited by the Examiner relating to the unpredictability of inter-genera transgenic behavior are not applicable to the intra-genus behavior of closely related *Caenorhabditis* species. The Examiner nevertheless maintains that the instant specification does not enable the production of a transgenic *Caenorhabditis* species.

The Examiner maintains that, absent any relevant teachings or guidance in the specification with regard to the production of any transgenic nematode as claimed, the art of transgenics is unpredictable and varies according to the particular host species and promoter/gene combinations with respect to the site of integration in the host genome, the expression of the transgene, and the resulting phenotype, one of skill in the art would not be able to rely on the state of the transgenic art for an attempt to produce LOV-1 transgenic nematodes. To support this contention, the Examiner again cites the references set forth in the Office Action of November 8, 2000, which include **Wall** (Theriogenology, 1996), **Houdebine** (Journal of Biotechnology, 1994), **Hammer *et al.*** (Journal of Animal Science, 1986), **Ebert *et al.*** (Molecular Endocrinology, 1988); **Mullins *et al.*** (Journal of Clinical Investigations, 1996), **Kappel *et al.*** (Current Opinion in Biotechnology, 1992) and **Strojek *et al.*** (Genetic Engineering, 1988). The Examiner further alleges that because the transgenic *Caenorhabditis* are not enabled, the claimed methods using transgenic *Caenorhabditis* are not enabled.

It is noted that in the Amendment filed in response to the Office Action mailed November 8, 2000, Applicant provided references (*e.g.*, Review by the *C. Elegans* Sequencing Consortium of the Washington University Genome Sequencing Center (*Science*, 282:2012-2018 (1998); Sommer *et al.*, Developmental Biology, 173:396-407 (1996)) demonstrating that nematode species that are related to *C. Elegans* are often used in experimental systems to

study development at the cellular, genetic and molecular levels, and to predict *C. Elegans* gene structure based on genomic sequence data from related *Caenorhabditis* nematode species. Hence, those of skill in the art are familiar with a variety of nematode species and manipulation of the genes in those species and recognize the relatedness among species of the genus *Caenorhabditis*.

On the other hand, the Examiner has provided no evidence that it is not possible to introduce a gene from one species of nematode into another. The references cited by the Examiner only describe the unpredictability of transgenic behavior as it relates to unrelated inter-genera predictions, not the *intra-genus* behavior of closely related species. Notwithstanding this, in the interest of advancing prosecution of claims to allowance, claims 27-32 and 42 are amended as being directed to transgenic nematodes of the *C. Elegans* species, thereby obviating the rejection with respect to enablement of transgenic *Caenorhabiditis* species and methods using transgenic *Caenorhabditis* species.

Lack of enablement rejection based on the alleged lack of working examples demonstrating transgenic nematodes, identification of genes and regulatory factors involved in polycystic kidney disease, and correlation between a nucleic acid isolated by the same method and polycystic kidney disease.

The Examiner further alleges that the specification describes the production of *C. elegans* that have been mutagenized and screened for a phenotype of interest; the specification allegedly has no working examples that correlate introduction and expression of a *lov-1* transgene into a *Caenorhabditis* and a corresponding phenotype that results from transgene expression. Furthermore, the Examiner alleges that the specification fails to provide working examples that demonstrate identification of genes and regulatory factors invol ved in polycystic kidney disease using mutagenized *C. elegans*, nor does it show a correlation between a nucleic acid isolated by the same method and polycystic kidney disease. This rejection is respectfully traversed. As discussed

in detail below, the specification provides working examples demonstrating a correlation between introduction and expression of a *lov-1* transgene into a *Caenorhabditis* and a corresponding phenotype that results from transgene expression. The specification also provides working examples that, when considered in light of what is known to those of skill in the art, demonstrate the ability to identify genes and regulatory factors involved in polycystic kidney disease using mutagenized *C. elegans*, and to establish a correlation between a nucleic acid isolated by the same method and polycystic kidney disease.

The specification teaches one of skill in the art to make and use the claimed products and methods without undue experimentation by (a) demonstrating the correlation between introduction and expression of a *lov-1* transgene into a *Caenorhabditis* and a corresponding phenotype that results from transgene expression; (b) demonstrating, in light of what is known to those of skill in the art, the identification of genes and regulatory factors involved in polycystic kidney disease using mutagenized *C. elegans*, and a correlation between a nucleic acid isolated by the same method and polycystic kidney disease.

Analysis

The scope of the claims

Claims 27-32 are directed to transgenic *Caenorhabditis elegans* nematodes that contain a vector that contains the nucleic acid encoding the *Caenorhabditis elegans* LOV-1 protein or a mutant thereof that results in altered mating behavior in *Caenorhabditis elegans*.

Claim 42 is directed to a transgenic Caenorhabditis elegans nematode, comprising the nucleic acid molecule of claim 15 (*i.e.*, an isolated nucleic acid molecule encoding a mutant *Caenorhabditis* LOV-1 protein which when expressed by a *C. elegans* nematode shows defective Lov and or response mating behaviors).

Claim 74 is directed to a method for identifying genes or regulatory factors involved in polycystic kidney diseases by mutagenizing transgenic *Caenorhabditis elegans* nematodes that contain a dominant negative *lov-1*

transgene and looking for offspring that demonstrate further loss in function and identifying any additional genes responsible for the loss. Claim 75 specifies that the genes are homologous mammalian genes.

Claim 76 is directed to a method for identifying regulators and factors necessary for synthesis and transport of *LOV-1* protein by preparing a transgenic *Caenorhabditis elegans* nematode that expresses a detectable marker linked to *LOV-1* protein, mutagenizing the nematode, selecting nematodes or offspring thereof that have altered patterns of expression of *LOV-1* and identifying the gene responsible for the alteration.

Claim 77 is a method for identifying transcriptional regulators of *lov-1* by preparing a transgenic *Caenorhabditis elegans* nematode that expresses a detectable marker linked to *LOV-1* protein, mutagenizing the nematode, selecting nematodes or offspring thereof that have altered levels of expression of the marker.

Claims 82-84 are directed to methods for identifying genes and regulatory factos involved in polycystic kidney disease by mutagenizing *Caenorhabditis elegans* nematodes, looking for clumping behavior on a lawn of bacteria, selecting males that do not exhibit clumping behavior, mutagenizing them and looking for restoration of wild-type behavior.

Thus, all of the claims specify that the gene used in the production of a transgenic nematode is a *Caenorhabditis elegans lov-1* gene, and the transgenic nematode is a *Caenorhabditis elegans* nematode. Further, the claims specify the behavior that is altered or restored to wild-type upon mutation of the wild-type or transgenic *C. elegans*.

It is respectfully submitted that it would not require undue experimentation to produce a transgenic *Caenorhabditis elegans* nematode, and to use mutagenized and/or transgenic nematodes in which expression of the *lov-1* gene is modulated to identify genes or regulatory factors involved in polycystic kidney disease.

Teachings of the specification

The specification describes identification and isolation of the *lov-1* gene from *C. Elegans*, the characterization of *lov-1* mutants, wild-type and mutant LOV-1 proteins encoded by the *lov-1* gene and mutants thereof, the discovery of a correlation between *lov-1* gene expression and observable mating behavior phenotypes, and the use of this discovery in methods to identify genes involved in the etiology of polycystic kidney disease.

The instant application describes and exemplifies in great detail methods for isolating nematode genes, for introducing mutations into nematode genes and for preparing transgenic nematode species. For example, Figure 2 and page 31, lines 3-22 of the specification describe the isolation and characterization of the exemplary nematode gene *lov-1* from the *C. elegans* nematode. Page 8, lines 4-8 of the specification describe that genes involved in the polycystic kidney disease pathway may be identified by mutagenizing normal males, selecting offspring that exhibit changes in mating behavior or mating efficiency and identifying the mutated genes. Page 36, lines 11-31 of the specification describe the isolation and characterization of the exemplary *C. elegans* knockout mutant *sy582* using the chemical mutagen EMS, and page 21, lines 34-38; page 36, line 32 to page 37, line 8 of the specification provide the standard methods by which nematode mutants may be obtained.

Further, the specification sets forth in great detail the production of transgenic nematodes. Page 9, lines 2-5 of the specification provides that transgenic nematodes can be produced by any method known to those of skill in the art, including, but not limited to, injection of the nucleic acid into the embryos or cells of the animal, and page 43, lines 1-3 of the specification provides that "precise protocols for culturing and nematodes, producing mutants and transgenics, and for observing behaviors are well known to those of skill in the art". The constructs used to prepare the transgenic nematodes are described, for example, at Figures 2 and 3 of the specification, in EXAMPLE 2 at

page 54 of the specification, which describes the production of transgenic nematodes carrying nematode-reporter fusion genes, at page 31, lines 3-14 of the specification, and at page 52, line 21 to page 53, line 3 of the specification.

Figure 2 and page 31, lines 3-14 of the specification describes the production of transgenic nematodes using various constructs that either alter the "location of vulva" and "response" behaviors in wild-type ("normal") males, or restore wild-type behavior in mutant nematodes, such as the exemplary mutant nematode *sy552* that has 30% of the "location of vulva" and "response" efficiency of wild-type males:

> The *lov-1* gene was cloned by genetic mapping and transformation rescue of the *sy552* behavioral defects (Fig. 2a). *mnDf2l/sy552, mnDf83/sy552* and *sy552/sy552* males are phenotypically indistinguishable; therefore, *sy522* is reduction or loss of function mutation in *lov-1*. This conclusion is supported by the observed recessive nature of *sy552*. **A 16.9 kb HindIII subclone (plov-1.1) of the cosmid ZK945 rescued response and Lov defects of *sy552* (Fig. 2a).** Both a 6.7 kb HindIII-BamHI fragment from plov-1.1 (plov-1::GFP1) and a 14.1 kb HindIII-StuI frameshift in plov-1.1 (plov-1.3) fail to rescue *sy552* defects (Fig. 2b) yet act in a dominant negative (DN) manner in wild-type males with respect to Lov behavior (Fig. 2c). **Wild-type males expressing either plov-1::GFP or plov-1.3 are Lov defective.** (emphasis added)

Page 48, lines 4-9 of the specification describes transgenic nematodes prepared using the construct plov-1.3 (plov-1.3 encodes a truncated LOV-1 protein lacking the polycystin block 2/channel domain), which has a dominant negative effect in transgenic nematodes affecting only the Lov (location of vulva) behavior and not the Response behavior. Further, as discussed below under "Working Examples", EXAMPLES 1 and 2 of the specification describe the production and use of various transgenic nematodes to study the expression of genes involved in mating behaviors, and the effect of the transgenes on such mating behaviors.

As described in the specification and as discussed with respect to "Knowledge of those of Skill in the Art" below, it is known to those of skill in

the art that nematodes are a model multicellular organism for studying the function of human genes in normal and disease states. For example, page 23, line 26 to page 24, line 16 of the specification states:

> Nematodes, particularly *C. elegans*, is one of the most thoroughly understood of all multicellular organisms. The biology of its nervous system, which contains 302 neurons, is well-documented. Many *C. elegans* genes used have counterparts in mammals, including humans. At least half of the C. elegans genes and proteins that have been characterized have structures and functions similar to mammalian genes. These include genes encode enzymes, proteins necessary for cell structure, cell surface receptors and genetic regulatory molecules.
> Animals from man to worm have most of their protein families in common and humans frequently have four to five close analogs of a protein family member, where worms have only one. **Essentially all genes and pathways shown to be important in cell-, developmental- and disease-biology have been found to be conserved between worm and human.** This conservation applies to the number and type of protein families, gene structure, the hierarchy of genes in genetic pathways and even gene regulation.
> A consequence of this conservation is that human genes can be inserted into the worm genome, to functionally replace the worm genes even in complex cell biological and signal transduction pathways. **Conversely, key worm genes identified using genetics can be used to trigger specific biochemical processes in human cells and to serve as models for the human genes.** (emphasis added)

Therefore, as described in the instant application, nematode genes that show a high degree of homology to the genes involved in human polycystic kidney disease and are associated with an identifiable phenotype such as specific defects in mating behavior may be used to study the polycystic kidney disease pathway, for identifying additional components of the pathway, and for use in drug screening assays to identify compounds affect the pathway and/or compounds that serve as leads for development of drugs for treatment of polycystic kidney disease. The specification also describes that, not only do the *lov-1* and *pkd-2* nematode genes have a high degree of homology to the genes involved in human polycystic kidney disease, but the pathways in which the

human and nematode genes are involved are similar. For example, page 29, line 28 to page 30, line 11 of the specification provides:

> This gene, *lov-1*, encodes a putative membrane protein with a mucin-like, serine-threonine rich amino terminus (Carraway *et al.* (1995) *Trends Glycoscience Glycotechnology 7*:31-44) followed by two blocks of homology to human polycystins encoded by the autosomal dominant polycystic kidney disease (ADPKD) genes (Torres *et al.* (1998) Current Opinion in Nephrology and *Hypertension 7*:159-169). LOV-1 and human PKD1 are 26% identical in block 1. Block 2 also shows 20% identity between LOV-1, all identified polycystins (PKD1, PKD2, and PKDL), and the family of voltage-activated channels (Torres *et al.* (1998) Current Opinion in Nephrology and *Hypertension 7*:159-169). Overall, LOV-1 is the closest *C. elegans* homolog of PKD1. The polycystin/channel domain (block 2) of LOV-1 is required for function. *Lov-1* is specially expressed in adult male sensory neurons of the rays, hook, and head, mediating response, Lov, and potentially chemotaxis to hermaphrodites, respectively (Liu *et al. Neuron 14*:79-89, Ward *et al.* (1975) *J. Comp. Neurol. 160*:313-337). **Localization of *lov-1* to neuronal cell bodies and ciliated sensory endings is consistent with a role in either chemo- and/or mechanosensory reception and signaling. Human PKD proteins might similarly be involved in sensory reception during osmoregulation, organogenesis and/or organ maintenance.** (emphasis added)

See also page 40, line 6 to page 41, line 6 of the specification, which provides:

> Neither the precise functions of the polycystins nor the molecular basis of kidney cystogenesis is known. **The results provided herein show that the homologs of the polycysins act together in a pathway, that appears to be a signal transduction pathway, in sensory neurons. It has been postulated that human polycystin 1 and polycystin 2 function as an ion channel (Torres *et al.* (1998) Current Opinion in Nephrology and *Hypertension 7*:159-169). Further supporting this conlusion, are the results of others that have indicated that human PKD2 is associated with the activity of a cation channel.** These results were obtained using cell-expression and electrophysiological approaches to examine the potential channel function of a protein called PCL (polycystin-like) that had been identified in the human expressed sequence-tag database by its sequence similarity with PKD2 (Chen *et al.* (1999) *Nature*

> *401*:383-386). PCL was expressed in *Xenopus oöcytes* by microinjecting synthetic mRNA and the channel properties were studied using the the two micro-electrrode voltage clamp and patch-clamp techniques. It was found that PCL is a non-selective cation channel that is permable to sodium, potassium and calcium. It is more permeable to calcium. Thus, PCL and PKD2 may be cation-channel subunits.
> **Hence, as shown herein, PKD1-related proteins act as receptors that regulate the activity PKD2-related proteins. The two proteins are part of a conserved pathway that appears to be a signalling mechanism in which the translocation of ions acts as a second messenger.** (emphasis added)

Furthermore, the specification sets forth assays, described below under "Working Examples", that correlate expression of *lov-1* nematode mutants with defective mating behaviors, and assays are set forth demonstrating how such correlation may be used to identify genes that are involved in the etiology of polycystic kidney disease and to provide treatments for polycystic kidney disease. Thus, the specification is fully enabling for the identification of nematode genes with an observable phenotype that provide a model for the study of human polycystic kidney disease, and for the production and/or assay of wild-type, mutagenized and transgenic nematodes that may be used to study the pathway of polycystic kidney disease and possible treatments therefor.

Level of skill

The level of skill in this art is recognized to be high (see, *e.g.*, Ex parte Forman, 230 USPQ 546 (Bd. Pat. App. & Int'f 1986)). The numerous articles and patents made of record in this application address a highly skilled audience and further evidence the high level of skill in this art.

Knowledge of those of skill in the art

At the time of the effective filing date of this application and before, the skilled artisan knew of standard methods for isolating and characterizing vertebrate homologs of nematode genes. For instance, Bargmann *et al.*, *Science*, 282:2028-2033 (1998), of record in the application's file history, discusses that the *C. Elegans* homologs of highly conserved neuronal genes and

human disease genes are open to standard methods for isolating mutations and characterizing gene networks by enhancer and suppressor analysis. Bargmann describes numerous examples (*e.g.*, neurotransmitter receptors, neurotransmitter synthesis and release pathways, G protein-coupled second messenger pathways) of *C. elegans* homologs of human genes that are shown to have a similar or identical function in *C. elegans* as they do in human beings. Brenner, *Genetics*, 77:71-94 (1974), also of record in the file history of the instant application, describes methods for the isolation, complementation and mapping of *C. Elegans* mutants. Brenner further describes the value of the simple multicellular organism *C. elegans* in determining the structure of the nervous system. A review by the *C. Elegans* Sequencing Consortium of the Washington University Genome Sequencing Center describes the utility of the complete genomic sequence of *C. Elegans* as a platform for investigating biology (*Science*, 282:2012-2018 (1998); of record in the file history of the instant application; hereinafter "*C. Elegans* Sequencing Consortium Review"). The *C. Elegans* Sequencing Consortium Review highlights the importance, known to those of skill in the art, of using a multi-cellular organism such as *C. Elegans* as a tool for comparison with and interpretation of other genomes, including the human genome (page 2016, column 2). The *C. Elegans* Sequencing Consortium Review also describes that "as expected from evolutionary relationships, there were substantially more protein similarities found between *C. elegans* and *H. sapiens* than between any other cross-species pairwise combination" (page 2014, column 1).

Thus, at the time of filing of the instant application, not only were the methods for isolating nematode genes, for introducing mutations into nematode genes, for preparing transgenic nematodes and for studying the expression of nematode genes known to those of skill in the art, but those of skill in the art had also recognized the value of the exemplary multicellular organism *Caenorhabditis* as a tool to study the genetic organization of other multicellular

organisms, particularly human beings, and the use of nematodes to identify genes involved in normal and disease conditions in human beings.

Predictability

As discussed above with respect to the knowledge of those of skill in the art and the teachings of the specification, the instant application employs standard methods that are known to those of skill in the art to isolate and clone nematode genes, to mutagenize nematodes, to prepare transgenic nematodes, and to study and treat human disease in which homologs and orthologs of nematode genes are implicated.

Presence of working examples

The specification provides working examples and descriptions for the production of mutant and transgenic nematodes, and for the use of mutant nematodes and transgenic nematodes in studying the etiology and identifying treatments for polycystic kidney disease. Examples are provided below:

1) EXAMPLE 1 at page 51 of the specification describes the mating behavior and mating efficiency assays that were used to identify the *C. elegans* orthologs of human polycystins, screening for mutants of the same, the genetic mapping of *lov-1* and the production of transgenic nematodes that rescued the defects in mating behavior of *lov-1*(*sy552*) mutants.

2) EXAMPLE 2 at page 54 of the specification describes the expression analyses of *lov-1* and *pkd-2* genes using *lov-1* or *pkd-2* fusion constructs with suitable reporter genes such as the fluorescent GFP. The fusion constructs were used to prepare transgenic nematodes that were then studied by fluorescence microscopy.

3) page 43, line 5 to page 44, line 29 of the specification describes assays that identify abnormal mating behaviors, particularly the lov and/or response behaviors, that may be used to detect components of the PKD pathway or compounds that affect the PKD pathway.

4) page 45, lines 1-22 of the specification and elsewhere throughout the specification describe mating efficiency assays used to identify nematodes displaying abnormal mating behaviors.

5) page 46, lines 1-24 of the specification describes the restoration of lov and/or response mating behaviors in *lov-1* mutant nematodes using suppressor and enhancer screens.

6) page 46, line 25 to page 47, line 8 of the specification describes the use of sensory assays as another avenue to study the PKD pathway, since *lov-1* and *pkd-2* genes were shown to be expressed in CEM neurons.

7) page 47, line 9 to page 48, line 16 of the specification describes assays using transgenic nematodes that are "dominant negative", *i.e.*, wild-type nematodes are altered using a transgene whose phenotype (*e.g.*, altered mating behavior) is manifested instead of the wild-type phenotype. Such transgenic nematodes are then used to identify mutations and/or compounds that inhibit or otherwise alter PKD function.

8) page 48, line 17 to page 50, line 2 of the specification describes assays to identify regulators and factors necessary for synthesis and transport of LOV-1 and/or PKD-2 proteins, assays for identifying transcriptional regulators of expression of *lov-1* and/or *pkd-2* genes, and a visual assay to identify *lov-1* and *pkd-2* mutant males, which, unlike wild-type males, do not exhibit "clumping" on a bacterial lawn.

Conclusion

As discussed above, the specification provides working examples showing the introduction and expression of a *lov-1* transgene into a *Caenorhabditis elegans* nematode and a corresponding phenotype, namely, altered mating behavior, that results from transgene expression. Further, the specification demonstrates, in light of what is known to those of skill in the art, the use of *C. elegans* as a model multi-cellular organism to study genes involved in human disease. Specifically, in light of what is known to those of skill in the

art, the specification provides working examples demonstrating the identification of genes and regulatory factors involved in polycystic kidney disease using mutagenized *C. elegans*, and a correlation between a nucleic acid isolated by the same method and polycystic kidney disease. Therefore, in light of the extensive teachings and examples in the specification, the high level of skill of those in this art, the knowledge of those of skill in the art and the breadth of the claims, it would not require undue experimentation for the skilled artisan to make and use the claimed transgenic *Caenorhabditis elegans* nematodes and to practice the claimed methods for the identification of genes and regulatory factors involved in polycystic kidney disease.

THE REJECTION OF CLAIMS 9-11 UNDER 35 U.S.C. §112, SECOND PARAGRAPH

Claims 9-11 are rejected under 35 U.S.C. 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter that applicants regard as the invention. The Examiner maintains that the term "gene" is indefinite because there is allegedly no clear consensus definition in the art accurately delimiting the term "gene" in view of alternative splicing and uncertainties surrounding the metes and bounds of cis-acting elements regulating mRNA expression. The Examiner alleges that although the claims as amended in the response filed May 8, 2000, recite that the gene encodes a LOV-1 protein, the term "gene" also encompasses intron/exon boundaries and promoter regions, which have not been defined by the claims.

It is respectfully submitted that claims 9-11, when read in light of the specification (*see* "Relevant Law" and "Analysis" below), adequately define the metes and bounds of the term "gene" as used in the claims. The specification provides the *lov-1* gene as defined by its regulatory regions, its intron/exon boundaries, and the LOV-1 protein encoded by the gene.

As discussed below, claims 9-11 are directed to a specific gene, the *lov-1* gene. Further, as discussed below, the specification defines the intron/exon boundaries, the promoter region and the expressed protein sequence of the *lov-1* gene in great detail.

Relevant Law

Claims are not read in a vacuum but instead are considered in light of the specification and the general understanding of the skilled artisan. *Rosemount Inc. v. Beckman Instruments, Inc.*, 727 F.2d 1540, 1547, 221 USPQ 1, 7 (Fed. Cir. 1984), *Caterpillar Tractor Co. v. Berco, S.P.A.*, 714 F.2d 1110, 1116, 219 USPQ 185, 188 (Fed. Cir. 1983). When one skilled in the art would understand all of the language in the claims when read in light of the specification, a claim is not indefinite.

35 U.S.C. § 112, second paragraph requires only reasonable precision in delineating the bounds of the claimed invention. Claim language is satisfactory if it reasonably apprises those of skill in the art of the bounds of the claimed invention and is as precise as the subject matter permits. *Shatterproof Glass Corp. v. Libby-Owens Ford Col.*, 758 F.2d 613, 624, 225 USPQ 634, 641 (Fed. Cir.), cert. dismissed, 106 S.Ct. 340 (1985).

The amount of detail required to be included in the claims depends on the particular subject matter and the prior art and is not to be viewed in the abstract, but in conjunction with whether the specification is in compliance with the first paragraph of 35 U.S.C. § 112. If the claims, read in light of the specification, reasonably apprise those skilled in the art of the utilization and scope of the invention, and if the language is as precise as the subject matter permits, the courts can demand no more:

> [i]t is not necessary that a claim recite each and every element needed for the practical utilization of the claimed subject matter (*Bendix Corp. v United States*, 600 F.2d 1364, 1369, 220 Ct. Cl. 507, 514, 204 USPQ 617, 621 (1979); See, also, *Carl Zeiss Stiftung v. Renishaw plc*, 20 USPQ2d 1094, 1101).

Analysis

With respect to claims 9-11, the claimed "gene" is the specific gene that is disclosed in the specification. The specification provides description of this gene, including intron/exon boundaries, coding sequence, and promoter region. Further, the specification sets forth in great detail the definition of the gene that claimed in claims 9-11. For example, SEQ ID No. 3 sets forth the complement (*i.e.*, the non-coding strand) of the *lov-1* gene from *C. elegans*, and SEQ ID No. 4 sets forth the sequence of amino acids of the protein (N-terminus to C-terminus)) encoded by the *lov-1* gene. Further, Figure 2 describes the intron-exon boundaries of the *lov-1* gene. As described, for example, at page 31, lines 18-28 of the specification:

> Figure 2b illustrates the intron-exon boundaries of the *lov-1* gene. Using RT-PCR with *lov-1* specific primers and *him*-5 mRNA, it was found that *lov-1* encodes one transcript corresponding to Genefinder-predicted ORFs, ZK945.10 and ZK945.9 (Fig. 2b), which had been thought to be two genes. *Lov-1* encodes a predicted 3178 amino acid membrane-bound protein (see SEQ ID Nos. 3 and 4) with a serine-threonine rich extracellular domain homologous to mucins (Carraway *et al.* (1995) *Trends Glycoscience Glycotechnology* 7:31-44), a polycystin homology block 1 (26% identity), and a carboxy terminal polycystin block 2 with 20% identity to polycystin proteins 1, 2, and 2, encoded by the PKD1, PKD2, and PKDL (polycystic kidney disease) genes, respectively (Fig. 2d).

See, also, page 34, lines 13-27 of the specification, which states:

> Figure 2b illustrates the intron-exon boundaries of the *lov-1* gene. Using RT-PCR with *lov-1* specific primers and *him*-5 mRNA, it was As noted above, Figure 2B depicts the *lov-1* genomic structure (exons shown as boxes, introns as lines). With reference to Figure 2B, the coding sequence in the gene set forth in SEQ ID No. 3 (noting that SEQ ID 3 sets forth the non-coding strand) is as follows:
>
> Complement (Join (12500...12685) - Exon A; (12266...12451) - Exon B; (12085...12217) - Exon C; (11683...11823) - Exon D; (11498...11637) - Exon E; (11128...11452) - Exon F; (10268...10899) - Exon G; (10138...10216) - Exon H; (9436...9983) - **Exon I**;

(9312...9392) - **Exon J**; (8685...9262) - **Exon K**;
(8557...8635) - Exon L; (7830...7997) - Exon M;
(6774...7786) - Exon N; (6648...6728) - Exon O;
(6305...6598) - Exon P; (6006...6255) - Exon Q;
(5732...5958) - Exon R; (4849...5076) - Exon S;
(4698...4799) - Exon T; (4383...4651) - Exon U;
(3336...4328) - Exon V; (2229...3094) - Exon W;
(1976...2181) - Exon X; (1635...1930) - Exon Y;
(1043...1591) - Exon Z; (625...999) - Exon AA;
(329...572) - Exon BB; (1...270) - Exon CC).

Further, page 35, lines 1-2 of the specification specifies that the sequence of the LOV-1 protein encoded by the *lov-1* gene is set forth in SEQ ID NO. 4, and Table 3 at page 35 of the specification specifies the location of the intron/exon boundaries of the isolated *lov-1* gene claimed herein with respect to Genbank database submissions of cosmids containing *C. elegans* genomic sequence.

In addition, the specification defines the promoter region of the *lov-1* gene. For example, Figures 3 and 4 and Example 2 of the specification describe the experiments that establish the promoter region of the *lov-1* gene. See, *e.g.*, page 37, lines 9-19 of the specification, which describes that the promoter region directing expression of a lov-1-GFP fusion protein is in the region within 2.8 kb of sequence upstream of the *lov-1* gene and 3.9 kb of *lov-1* gene sequence (this 6.7 kb sequence was used to construct the plov-1::GFP1 fusion protein, and it directed expression of the fusion protein in male-specific neurons):

> **Expression patterns of *lov-1***
> To elucidate the cells in which *lov-1* acts to affect male mating behaviors, the expression pattern of *lov-1*-::GFP reporter genes was examined (see Example 2 and Fig. 4). These experiments reveal regulatory regions in the *lov-1* gene. A partial translational fusion containing 2.8 kb of upstream sequence and 3.9 kb of *lov-1* (plov-1::GFP1) directs male-specific expression in male-specific sensory neurons (Fig. 2c and Fig. 4). Conversely, shorter versions of plov-1::GFP1 are not expressed in the same set of male-specific neurons nor

exclusively in male-specific sensory neurons and do not act as DNs (Fig. 2c).

Further, Example 2 at page 54 of the specification describes that the aformentioned region involved in regulating the expression of lov-1, *i.e.*, 2.8 kb of upstream sequence and 3.9 kb of *lov-1* gene sequence is the *Hind*III-*Bam*HI fragment of plov-1.1, described in Figure 2a of the specification as a 16.9 kb HindIII subclone of the cosmid ZK945 (Genbank Accession No. Z48544, disclosed at page 36, line 10 of the specification). In addition, Figures 3 and 4 and Example 2 of the specification show that the shorter *Hind*III-*Hpa*I fragment of plov-1.1, used to construct the plov-1::GFP2 fusion protein and containing only the 2.8 kb of upstream sequence without any of the *lov-1* coding sequence does not direct expression of the plov-1::GFP2 fusion protein. Similarly, fusion proteins plov-1::GFP3, constructed using a *Sac*I (Klenow filled-in and religated) deletion of plov-1::GFP1 that contains about 1 kb of upstream sequence and the sequence containing exons G through K of *lov-1*; and plov-1::GFP4, constructed using a *Hind*III-*Hpa*I (Klenow filled-in and religated) deletion of plov-1::GFP1 that is the sequence containing exons A though K of *lov-1* and none of the upstream sequence, are not expressed. Thus, the specification describes that the *lov-1* promoter sequence is (i) within the region containing 2.8 kb of sequence upstream of the *lov-1* gene and 3.9 kb of sequence containing exons A through K of the *lov-1* gene; and (ii) the *lov-1* coding sequence containing exons A through K alone, the 2.8 kb upstream sequence alone, or 1 kb of upstream sequence combined with the sequence containing exons G through K of the *lov-1* gene are insufficient to direct gene expression of the fusion constructs.

The experiments above demonstrate that when the 2.8 kb sequence upstream of the *lov-1* gene is present 5′ of the *lov-1* gene, expression is obtained. As discussed above, all of the sequence information pertaining to the intron/exon boundaries, the coding sequence, and the expression-regulating promoter and other sequences of the *lov-1* gene are described and/or are incorporated by reference in the specification. Accordingly, it is respectfully

submitted that in light of the specification and what is known to those of skill in the art, the term "gene" as used in claims 9-11 to define a gene encoding a LOV-1 protein includes the promoter and the intron/exon boundaries, and is therefore not indefinite. Therefore, reconsideration and withdrawal of this rejection is respectfully requested.

THE REJECTION OF CLAIMS 1, 5, 7, 9-11 and 15-17 UNDER 35 U.S.C. § 102

Claims 1, 5, 7, 9-11 and 15-17 are rejected under 35 U.S.C. 102(b) as being allegedly anticipated by Wilson et al., (Nature 368:32-38, 1994) for reasons of record. The Examiner alleges that although Applicant has argued that Wilson does not disclosed the nucleotide sequence set forth in SEQ ID NO. 3, nor the 3178 amino acid LOV-1 protein, nor the coding regions and intron/exon boundaries of *lov-1*, the rejection is maintained because Wilson allegedly discloses a sequence that has 100% local similarity to the nucleotide sequence set forth in SEQ ID NO. 3. The Examiner contends that since the sequence of Wilson and SEQ ID NO. 3 allegedly share 100% local similarity, the sequence of Wilson comprises that of SEQ ID NO. 3. The Examiner further contends that since the sequence of Wilson allegedly shares 100% identity with that of SEQ ID NO. 3, it is inherent that the sequence of Wilson encodes the same amino acid sequence as that encoded by SEQ ID. NO. 3, and, furthermore, that the Wilson sequence and SEQ ID NO. 3 will hybridize to each other. This rejection is respectfully traversed. It is respectfully submitted that this rejection is rendered moot with respect to Claim 7, which was cancelled in the Amendment filed May 8, 2001.

Relevant law

Anticipation requires the disclosure in a single prior art reference of each element of the claim under consideration. In re Spada, 15 USPQ2d 1655 (Fed. Cir, 1990), In re Bond, 15 USPQ 1566 (Fed. Cir. 1990), Soundscriber Corp. v. U.S.. 360 F.2d 954, 148 USPQ 298, 301, adopted 149 USPQ 640 (Ct. Cl.)

1966. See, also, Richardson v. Suzuki Motor Co., 868 F.2d 1226, 1236, 9 USPQ2d 1913,1920 (Fed. Cir.), cert. denied, 110 S.Ct. 154 (1989). "[A]ll limitations in the claims must be found in the reference, since the claims measure the invention". In re Lang, 644 F.2d 856, 862, 209 USPQ 288, 293 (CCPA 1981). Moreover it is incumbent on Examiner to identify wherein each and every facet of the claimed invention is disclosed in the reference. Lindemann Maschinen-fabrik Gmbh v. American Hoist and Derrick Co., 730 F.2d 1452, 221 USPQ 481 (Fed. Cir. 1984).

Further, the reference must describe the invention as claimed sufficiently to have placed a person of ordinary skill in the art in possession of the invention. Prior art does not anticipate a thing or process unless it is enabling; an anticipatory publication must describe the claimed invention with sufficient clarity and specificity so that one skilled in the relevant art could practice the subject matter of the patent without assistance from the patent claimed to have been anticipated Columbia Broadcasting System v. Sylvania Elec. Products, Inc., 415 F.2d 719, 735, 162 USPQ 577 (1st Cir.1968) cert. denied, 396 U.S. 1061, 164 USPQ 321 (1970).

"Before any publication can amount to a statutory bar to the grant of a patent, its disclosure must be such that a skilled artisan could take its teachings in combination with his own knowledge of the particular art and be in possession of the invention." Titanium Metals crp. v Mossinghoff, 603 F.Supp. 87,0, 225 USPQ 673 (1984) quoting In re Application of Le Grice 49 CCPA 1124, 301 F.2d 9333

The claims

Claim 1 is directed to an isolated nucleic acid molecule comprising a sequence of nucleotides selected from among (a) a sequence of nucleotides encoding a *Caenorhabditis* nematode LOV-1 protein and encoding the sequence of amino acids encoded by the complement of the sequence set forth in SEQ ID NO. 3; (b) a sequence of nucleotides that is the complement of a sequence of

nucleotides set forth in SEQ ID. NO 3 and that encodes a *Caenorhabditis* LOV-1 protein, or a complement thereof; (c) a sequence of nucleotides that encodes a *Caenorhabditis lov-1* gene and that hybridizes to at least one of the exons of SEQ ID NO. 3 under conditions of at least moderate stringency and is present in a *Caenorhabditis* nematode genome, or (d) a degenerate nucleotide sequence of SEQ ID NO. 3, and a *C. Elegans* nematode expressing the protein exhibits normal location of vulva and response sensory behaviors. Claim 5 is directed to the nucleic acid molecule of claim 1 that encodes the amino acid sequence set forth in SEQ ID NO. 4. Claim 9 is directed to an isolated gene comprising the nucleic acid molecule of claim 1, and claims 10-11 further define the isolated gene of claim 9 as comprising homologous or heterologous transcriptional control elements. Claims 15-17 are directed to isolated nucleic acid molecules that encode mutant forms of the protein encoded by the molecule of claim 1 where a *Caenorhabditis elegans* expressing such mutant protein exhibits an alteration in one or both of the location of vulva and/or response phenotype.

Differences between the disclosure of Wilson et al. and the claimed subject matter

Wilson *et al.* discloses *Caenorhabditis elegans* clones **from chromosome III**, and the GENEFINDER-predicted open reading frames therein. The GENEFINDER program employed in the disclosure of Wilson only identifies likely genes **of chromosome III,** based on a comparison of the sequence data set forth in Wilson with public sequence databases. Wilson does not disclose the isolated genes, nor mutants thereof, claimed in the instant application, which are genes **from chromosome II** of *C. Elegans*. The Examiner's sequence search provided with the previous Office Action mailed November 8, 2000, is the sequence of nucleotides corresponding to the *C. elegans* cosmid ZK945, which contains *C. elegans* genomic sequence from chromosome II of *C. elegans* (*see* Genbank sequence submission, attached hereto).

The genomic sequence of the *C. elegans* cosmid ZK945 does not have 100% local sequence similarity to that set forth in SEQ ID NO. 3. The ZK945

Genbank sequence data provides only 12,222 bases of the sequence set forth in SEQ ID NO. 3. SEQ ID NO. 3 contains genomic sequence from more than one cosmid: 12,222 bases of sequence from cosmid ZK945 comprising exons C through Z and exon AA-CC of the *lov-1* gene, and the remainder from cosmid F27E5 comprising exons A and B of the *lov-1* gene, for a total of 12,685 bases of sequence as set forth in SEQ ID NO. 3. The ZK945 sequence does not comprise the entire sequence set forth in SEQ ID NO. 3, nor the entire coding sequence of the *lov-1* gene as discovered and claimed in the instant application. SEQ ID NO. 3 contains additional sequence comprising some of the exons of the *lov-1* gene that is not present in the cosmid ZK945.

The 12,222 bases of the *C. elegans* cosmid ZK945 sequence data that is 100% similar to part of the sequence set forth in SEQ ID. NO. 3 does not anticipate all of the elements of claim 1, nor of its dependent claims because: (a) it does not contain all of the genomic sequence or coding sequence comprising the *lov-1* gene that is set forth in SEQ ID NO. 3; (b) it does not encode the sequence of amino acids encoded by the complement of the sequence of nucleotides set forth in SEQ ID NO. 3 because it does not contain all of the coding sequence set forth in SEQ ID NO. 3; (c) it is not the complement of the sequence of nucleotides set forth in SEQ ID NO. 3. Furthermore, since the reference does not disclose the full-length sequence of the gene nor any utility or associated phenotype it does not meet limitations (c) or (d) of claim 1.

Furthermore, the cited reference does not provide a utility for the sequences disclosed therein; such showing is required for a reference to be novelty defeating. No use is provided for any sequence.

The GENEFINDER program employed in the disclosure of the Genbank sequence data submission for cosmid ZK945 only identifies likely genes, based on a comparison of the ZK945 sequence data with other publicly available sequence data. At the time of the Genbank sequence submission of the ZK945

sequence data and prior to the isolation of the *lov-1* gene as claimed in the instant application, the GENEFINDER program predicted two separate genes: "ZK945.9" and "ZK945.10". It was the actual isolation and characterization of the *lov-1* gene as claimed in the instant application that led to the discovery that *lov-1* encodes a single transcript corresponding to the GENEFINDER-predicted open reading frames "ZK945.9" and "ZK945.10". As shown in the instant application, the intron/exon boundaries of isolated genes are not identical to that predicted by computer analysis of the genomic clones in the databases. The cosmid that has 100% local similarity does not encompass the entire *lov-1* gene.

As shown and stated in the application (page 33):

> SEQ ID NO. 3 is the complement of the genomic sequence of the *lov-1* gene. It includes open reading frames (ORFs) between nucleotides 15760 to 27880 of cosmid ZK945 (nucleotides 1 to 12121 of SEQ ID NO.3) and nucleotides 1-564 of cosmid F27E5 (nucleotides 12122 to 12685 of SEQ ID NO.3). **It was found herein, however, that ZK945 and F27E5 overlap from nucleotides 27881 to 27981 and nucleotides 1 to 101, respectively (the overlap region includes nucleotides 12122 to 12222 in SEQ ID NO.3), thereby providing a single, rather than two, ORFs** (emphasis added).

Figure 2b illustrates the intron-exon boundaries of the *lov-1* gene and TABLE 3 provides a summary of their locations with reference to the Sequence Listing. Using RT-PCR with *lov-1* specific primers and *him*-5 mRNA, it was found that *lov-1* encodes one transcript corresponding to Genefinder-predicted ORFs, ZK945.10 and ZK945.9 (Fig. 2b), which had been thought to be two genes. *Lov-1* encodes a predicted 3178 amino acid membrane-bound protein (see SEQ ID Nos. 3 and 4) with a serine-threonine rich extracellular domain homologous to mucins (Carraway *et al.* (1995) *Trends Glycoscience Glycotechnology* 7:31-44), a polycystin homology block 1 (26% identity), and a carboxy terminal polycystin block 2 with 20% identity to polycystin proteins 1, 2, and 2, encoded by the PKD1, PKD2, and PKDL (polycystic kidney disease) genes, respectively (Fig. 2d).

Furthermore, exons I, J and K were not predicted by GENEFINDER but were identified in the isolated *lov-1* gene (see specification at page 33, line 20 to page 34, line 12), showing that *lov-1* encodes a single transcript rather than what was predicted to be two transcripts. As shown in the application (see, *e.g.*, pages 32 to 35), it was found that *lov-1* encodes one transcript corresponding to Genefinder-predicted ORFs, ZK945.10 and ZK945.9 (Fig. 2b), which had been thought to be two genes:

> DNA sequence analysis of RT-PCR generated cDNA clones from *him-5(e1490)* RNA revealed three exons (**exons I, J and K** in Figure 2B) in the junction between ZK945.10 and ZK945.9: one from nucleotides 25195 to 25742 of the ZK945 cosmid (nucleotides 9436 to 9983 of SEQ ID NO. 3); a second from nucleotides 25071 to 25151 of the ZK945 cosmid (nucleotides 9312 to 9392 of SEQ ID NO. 3); and a third initiating at position 25021 in the ZK945 cosmid (nucleotide 9262 of SEQ ID NO. 3). This demonstrated that the *lov-1* gene encodes one large transcript corresponding to ORFs in ZK945.10 and ZK945.9, spanning what had previously been thought to encode two proteins.

Lov-1 encodes a predicted 3178 amino acid membrane-bound protein that is not described in the Wilson disclosure. The ZK945 sequence data does not describe a single ORF that encodes a 3178 amino acid protein. Hence, the Genbank sequence submission does not provide the *lov-1* gene nor suggest the instantly claimed gene. Therefore, the GENEFINDER-predicted open reading frames disclosed in the Genbank sequence submission of the *C. elegans* cosmid ZK945 do not constitute the isolated nucleic acid molecules claimed in the instant application.

Neither the Wilson reference nor the Genbank sequence data for ZK945 discloses the isolated genes, or mutants thereof, claimed in the instant application. Furthermore, the sequence information set forth in Wilson and the Genbank ZK945 sequence submission does not teach or suggest a mutation in the sequence that results in a gene that when expressed in a nematode results in altered mating behavior. Neither the Wilson disclosure nor the Genbank

sequence data for *C. elegans* cosmid ZK945 provides any insights regarding the function of the *lov-1* gene, nor do they teach or suggest any mutations thereof.

As discussed above, Wilson does not provide any sequence data for the *lov-1* (on chromosome II) genomic sequence; Wilson only provides sequence data from chromosome III of *C. elegans*. Further, the Genbank sequence data from *C. elegans* cosmid ZK945 does not disclose the sequence set forth in SEQ ID NO. 3, nor the *lov-1* coding sequence, nor a utility for the *lov-1* gene. Therefore, since anticipation requires that a reference teach all elements as claimed and must provide a utility for a product, neither Wilson et al. nor the Genbank sequence data for cosmid ZK945 anticipate any of claims 1, 5, 9-11 and 15-17.

* * *

In view of the above amendments and remarks, reconsideration and allowance of the application are respectfully requested.

Respectfully submitted,
HELLER EHRMAN WHITE & McAULIFFE LLP

By: _____
Stephanie L. Seidman
Registration No. 33,779

Attorney Docket No. 18021-2919
Address all correspondence to:
HELLER EHRMAN WHITE & McAULIFFE LLP
4350 La Jolla Village Drive, 6th Floor
San Diego, CA 92122
Telephone: 858 450-8400
Facsimile: 858 587-5360
email:sseidman@HEWM.com

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Sternberg *et al.*

Serial No.: 09/479,467

Filed: January 06, 2000

For: POLYCYSTIC KIDNEY DISEASE GENE HOMOLOGS REQUIRED FOR MALE MATING BEHAVIOR IN NEMATODES AND ASSAYS BASED THEREON

Group Art Unit: 1632

Examiner: P. Paras, Jr.

I hereby certify that this paper and the attached papers are being deposited with the United States Postal Service as first class mail in an envelope addressed to:
Commissioner for Patents
Washington, D.C. 20231, on this date.

10/26/01
Date

Stephanie Seidman

MARKED UP CLAIMS (37 C.F.R. § 1.121)

Please amend claims 9, 27, 28, 29, 31, 32, 42, 76 and 77 as follows:

9. (Amended twice) An isolated gene, comprising the nucleic acid molecule of claim 1 that encodes a *Caenorhabditis elegans* [nematode] LOV-1 protein and that comprises the sequence of amino acids set forth in SEQ ID No. 4 [, comprising the nucleic acid molecule of claim 1].

27. (Amended twice) A transgenic *Caenorhabditis elegans* species nematode, comprising the vector of claim 26.

28. (Amended) The transgenic nematode of claim 27, wherein [in] the vector is maintained [extrachromsomally] extrachromosomally.

29. (Amended twice) The transgenic nematode of claim 27, wherein[:

the nematode is *Caenorhabditis elegans* (*C. elegans*); and]

the vector or a gene-encoding portion is integrated into the *C. elegans* genome.

31. (Amended twice) The transgenic nematode of claim 27, wherein:

the nucleic acid molecule encodes a mutant *LOV-1* protein;

a nematode expressing the mutant protein exhibits defective mating behavior; and

a nematode that expresses such defect exhibits one or both of an altered location of vulva (Lov) and response phenotype.

32. (Amended twice) The transgenic nematode of claim 30, wherein:

the nucleic acid molecule encodes a mutant *LOV-1* protein;

a nematode expressing the mutant protein exhibits defective mating behavior; and

a nematode that expresses such defect exhibits one or both of an altered location of vulva (Lov) and response phenotype.

42. (Amended twice) A transgenic *Caenorhabditis elegans* nematode, comprising the nucleic acid molecule of claim 15.

76. (Amended twice) A method for identifying regulators and factors necessary for synthesis and transport of *LOV-1* protein[;], comprising:

preparing a transgenic *Caenorhabditis elegans* nematode that expresses a detectable marker linked to *LOV-1* protein;

mutagenizing the nematode;

selecting nematodes or offspring thereof that have altered patterns of expression of *LOV-1*; and

identifying the gene responsible for the alteration.

77. (Amended twice) A method for identifying transcriptional regulators of *lov-1*, comprising:

preparing a transgenic *Caenorhabditis elegans* nematode that expresses a detectable marker linked to *LOV-1* protein;

mutagenizing the nematode; and

selecting nematodes or offspring thereof that have altered levels of expression of the protein.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Sternberg *et al.*

Serial No.: 09/479,467

Filed: January 6, 2000

For: POLYCYSTIC KIDNEY DISEASE HOMOLOGS REQUIRED FOR MALE MATING BEHAVIOR IN NEMATODES AND ASSAYS BASED THEREON

Art Unit: 1632

Examiner: P. Paras, Jr.

I hereby certify that this paper and the attached papers are being deposited with the United States Postal Service as first class mail in an envelope addressed to:

Commissioner for Patents,
Washington, D.C. 20231, on this date.

10/26/01
Date

Stephanie Seidman

ATTACHMENT TO RESPONSE TO OFFICE ACTION

1. Supporting reference:

   C. elegans cosmid ZK945, complete sequence from GenBank database (Accession No. Z48544)

☐ 1: Z48544. Caenorhabditis el... [gi:695493]


```
LOCUS       CEZK945     27981 bp    DNA             INV       20-JUN-2001
DEFINITION  Caenorhabditis elegans cosmid ZK945, complete sequence.
ACCESSION   Z48544
VERSION     Z48544.1  GI:695493
KEYWORDS    HTG; ARD1; Esterase; Mucin; Polycistic kidney disease protein 1;
            Proteasome component(A-type); Pumilio.
SOURCE      Caenorhabditis elegans.
  ORGANISM  Caenorhabditis elegans
            Eukaryota; Metazoa; Nematoda; Chromadorea; Rhabditida;
            Rhabditoidea; Rhabditidae; Peloderinae; Caenorhabditis.
REFERENCE   1  (bases 1 to 27981)
  AUTHORS   none.
  TITLE     Genome sequence of the nematode C. elegans: a platform for
            investigating biology. The C. elegans Sequencing Consortium
  JOURNAL   Science 282 (5396), 2012-2018 (1998)
  MEDLINE   99069613
  REMARK    The C.elegans Sequencing Consortium.
REFERENCE   2  (bases 1 to 27981)
  AUTHORS   Wilkinson,J.
  TITLE     Direct Submission
  JOURNAL   Submitted (01-MAR-1995) Nematode Sequencing Project, Sanger Centre,
            Hinxton, Cambridge CB10 1RQ, England and Department of Genetics,
            Washington University, St. Louis, MO 63110, USA. E-mail:
            jes@sanger.ac.uk or rw@nematode.wustl.edu
COMMENT     Coding sequences below are predicted from computer analysis, using
            predictions from Genefinder (P. Green, U. Washington), and other
            available information.
            Current sequence finishing criteria for the C. elegans genome
            sequencing consortium are that all bases are either sequenced
            unambiguously on both strands, or on a single strand with both a
            dye primer and dye terminator reaction, from distinct subclones.
            Exceptions are indicated by an explicit note.
            IMPORTANT: This sequence is not the entire insert of clone ZK945.
            It may be shorter because we only sequence overlapping sections
            once, or longer because we arrange for a small overlap between
            neighbouring submissions.
            The true left end of clone ZK945 is at 1 in this sequence. The true
            right end of clone ZK945 is at 8882 in
            sequence Z48582.
            The true left end of clone F27E5 is at 27881 in this sequence. The
            true right end of clone C18D1 is at 2079 in this sequence. The
            start of this sequence (1..104) overlaps with the end of sequence
            Z48543.
            The end of this sequence (27881..27981) overlaps with the start of
            sequence Z48582.
            For a graphical representation of this sequence and its analysis
            see:- http://wormbase.sanger.ac.uk/perl/ace/elegans/seq/sequence?
            name=ZK945.
```

```
FEATURES             Location/Qualifiers
     source          1..27981
                     /organism="Caenorhabditis elegans"
                     /db_xref="taxon:6239"
                     /chromosome="II"
                     /clone="ZK945"
     gene            join(1357..1454,2626..2766,3401..3695,4236..4898,
                     4947..5171)
                     /gene="ZK945.1"
     CDS             join(1357..1454,2626..2766,3401..3695,4236..4898,
                     4947..5171)
                     /gene="ZK945.1"
                     /note="similar to esterase
                     cDNA EST EMBL:T02204 comes from this gene
                     cDNA EST yk56f2.5 comes from this gene
                     cDNA EST yk206h6.3 comes from this gene
                     cDNA EST yk206h6.5 comes from this gene
                     cDNA EST yk299e8.3 comes from this gene
                     cDNA EST yk299e8.5 comes from this gene
                     cDNA EST yk302d10.3 comes from this gene
                     cDNA EST yk302d10.5 comes from this gene
                     cDNA EST yk387d8.3 comes from this gene
                     cDNA EST yk387d8.5 comes from this gene"
                     /codon_start=1
                     /protein_id="CAA88435.1"
                     /db_xref="GI:3881886"
                     /db_xref="SWISS-PROT:Q09621"
                     /translation="MDAMEDKGETEAENVVKLETGSSRRLLIYGIASILAVSGAWLVV
                     ATTVDSLACFIEGEMHLDNLVGHVAPGYEKVEKVFRRNFADGWEREGASITVYHKDRV
                     IVDLQGGYADKASGRKWTPDTRTVVFSTTKAVGAVCVAMLVDRGHISYDDKMSKIWPE
                     FAQNGKENITIDWLMSHRAGLAALDMPITIEDANDFEKMSEVIASQKPNWEPGTKSGY
                     HAITYGWIVDQIVRRSDPKGRSVGRFFKEEVADVHGIDFHIGLPPSEEHTVSRLSMPS
                     TLHLVREIVHDPRVLIVLAVFNLRPPNSIARKIAANPTWFKLEQDVNTFNNPTLHAME
                     QVAALGITKSRDLARLFSLVQQGKLFSTELLEKFRAPQVQGIDEVVMTPLPKGHGFLY
                     ERHPMGGKKWLVGHPGYGGSTVMMDLEDGITIAYVSNGLKTGMGELTRTYRHLRDSVF
                     ECLEKQKTGQSVMIEEAVQAVAA"
     gene            complement(join(5458..6057,6103..6215,6265..6334))
                     /gene="ZK945.2"
     CDS             complement(join(5458..6057,6103..6215,6265..6334))
                     /gene="ZK945.2"
                     /note="contains similarity to Pfam domain: PF00227
                     (Proteasome A-type and B-type), Score=200.0,
                     E-value=1.2e-56, N=1
                     cDNA EST yk162f6.5 comes from this gene
                     cDNA EST yk162f6.3 comes from this gene
                     cDNA EST yk404c9.3 comes from this gene
                     cDNA EST yk404c9.5 comes from this gene
                     cDNA EST yk478g11.3 comes from this gene
                     cDNA EST yk478g11.5 comes from this gene"
                     /codon_start=1
                     /protein_id="CAA88436.1"
                     /db_xref="GI:3881887"
                     /db_xref="SWISS-PROT:Q09583"
                     /translation="MSSIGTGYDLAASTFSPDGRIFQVEYAQKAVDNAGTMIAIRGKN
                     GVVVVADKLISSKLYTDNANPRMFNVNDNVGVAVAGNYPDGFALKNYAYGEAMKWLKD
                     YREPMPIQNIANSVAEYIHIHTLGISRPFGAGAFFMSWNKQTGGRLFLVEPSGLNYEY
                     KAWAVGKHRQAAKAEIEKLKIEELDVNQLVKEAARIIMVVRDENKDKNVQIEMGWVGE
                     QTNGKYEEVPSEVVTAAEEWAIASLTRTTWTIESFSCIYSHF"
     gene            join(6810..6929,6980..7282,7330..7834,7887..8146,
                     8193..8892,8940..9352)
                     /gene="ZK945.3"
     CDS             join(6810..6929,6980..7282,7330..7834,7887..8146,
                     8193..8892,8940..9352)
                     /gene="ZK945.3"
```

```
                     /note="similar to pumilio-repeat like domain
                     cDNA EST yk38f12.5 comes from this gene
                     cDNA EST CEMSC57F comes from this gene
                     cDNA EST EMBL:T00709 comes from this gene
                     cDNA EST yk38f12.3 comes from this gene
                     cDNA EST yk36f9.3 comes from this gene
                     cDNA EST yk36f9.5 comes from this gene
                     cDNA EST yk128e4.3 comes from this gene
                     cDNA EST yk49a7.3 comes from this gene
                     cDNA EST yk80e5.5 comes from this gene
                     cDNA EST yk49a7.5 comes from this gene
                     cDNA EST yk54a9.3 comes from this gene
                     cDNA EST yk80e5.3 comes from this gene
                     cDNA EST yk54a9.5 comes from this gene
                     cDNA EST yk128e4.5 comes from this gene
                     cDNA EST yk50b10.3 comes from this gene
                     cDNA EST yk50b10.5 comes from this gene
                     cDNA EST yk488h11.3 comes from this gene
                     cDNA EST yk488h11.5 comes from this gene
                     cDNA EST yk395d3.3 comes from this gene
                     cDNA EST yk395d3.5 comes from this gene
                     cDNA EST yk311b12.3 comes from this gene
                     cDNA EST yk311b12.5 comes from this gene
                     cDNA EST yk305a6.3 comes from this gene
                     cDNA EST yk305a6.5 comes from this gene
                     cDNA EST yk209a12.3 comes from this gene
                     cDNA EST yk209a12.5 comes from this gene
                     cDNA EST yk163f7.5 comes from this gene
                     cDNA EST yk318h4.5 comes from this gene
                     cDNA EST yk408e6.5 comes from this gene
                     cDNA EST yk414f10.5 comes from this gene
                     cDNA EST yk431c2.5 comes from this gene
                     cDNA EST yk462b11.5 comes from this gene
                     cDNA EST yk573f7.3 comes from this gene
                     cDNA EST yk621a8.3 comes from this gene
                     cDNA EST yk636g2.3 comes from this gene
                     cDNA EST yk573f7.5 comes from this gene
                     cDNA EST yk621a8.5 comes from this gene
                     cDNA EST yk627b7.5 comes from this gene
                     cDNA EST yk636g2.5 comes from this gene"
                     /codon_start=1
                     /protein_id="CAA88437.1"
                     /db_xref="GI:3881888"
                     /db_xref="SWISS-PROT:Q09622"
                     /translation="MVKLDDKNKKFKGKKKVKNVLEKKAKGLKLNKVDRKRIVKIEEK
                     AALKSKVDKAVKDELERLKKSSSTSVFDNDGTRDSLCSESSFGSQPAPKKKSKKVLFS
                     GELEHVKVFDKRVQDLQIKPSEASPGRGILRSPLDKKVKKLAKVKTVKVAQEEEEEHS
                     APPKKKVKVNAEKAVASEPADDENLESVDEQAGGDESHIDIPTLKRKRVAIQVTKSVK
                     EQLLNMPRKERKAFLKELKLKRKPEGARAQKCKELWEKIRMGKTPKAEKDTAVHELYG
                     LVKGHAAKLIYAHDTSRVIECLVATEREGIINNLFNELTPEIVRMSKNVYSKFFVKKM
                     LKNGTKEQRDIIINAFRGHAPTLLRIKHAAEVLEYAYNDFANAHQRYNIITEFYGKEF
                     ILFREDNIRSLTEILAEKPEKKVVILKHLDEVIGAVNEKETLRLSILHKLMLDFFDNC
                     DEEKKINLLDSLKDKIPEFIHTPDGAKLAIKLIWFAPVKERKLIVKNFKDLSVKAAME
                     HYGHRVLLALFDTVDDTVLLNKVIVSELANEMKKLIEDDWGEKVIHYLVHPRDGRGID
                     KREITFLAEGDSNPHSKKTQKDRYGQLYAGITENLYPYLAANFEELVFEANKSKFVAA
                     CLETTSSFDLFDRQVPAEARKSCNQAIVELAKKDFVPMDQEGFHIIEHQSGNFILMAV
                     MRCDAALQEDERLSVALAEGLTSKQLGSWVTCNRGCHVLLKMLQVGGPKVIEKLKASI
                     SRKHLDGYNSKGANLLKAQLDGNVKK"
gene                 complement(join(9594..9850,9899..9978,10023..10086,
                     10134..10500))
                     /gene="ZK945.4"
CDS                  complement(join(9594..9850,9899..9978,10023..10086,
                     10134..10500))
                     /gene="ZK945.4"
```

```
                     /codon_start=1
                     /protein_id="CAA88438.1"
                     /db_xref="GI:3881889"
                     /db_xref="SWISS-PROT:Q09381"
                     /translation="MDQAIKVLENEVVKRVRVLEYKISNQKLDLDWLQKNKDAIVKLS
                     ALPNMKLVQRKWELEVTVKRIEKDSAVRRPGIELYLKSLRSVIYFIEFLADCSTCIVH
                     VLSQRPLQIEMIPAFRLEIRECHRNEVRKFIENHSTRISSRSNILRYNCDFLEIIDRT
                     EDLTIYSEGLRLIMIVDLLDGDRDRYFVALEQLEEAVAYEKIIVGLKSYSRGHGEAAS
                     NFLTKLADLHNKMPKITVVVNVDRSEDIEKIVNESII"
gene                 complement(join(11096..11465,11747..12038,12087..12177))
                     /gene="ZK945.5"
CDS                  complement(join(11096..11465,11747..12038,12087..12177))
                     /gene="ZK945.5"
                     /note="similar to ARD1
                     cDNA EST yk600b5.5 comes from this gene"
                     /codon_start=1
                     /protein_id="CAA88443.3"
                     /db_xref="GI:9665270"
                     /db_xref="SWISS-PROT:Q09623"
                     /translation="MNMLRCFPECGICGQEYSEDEKLLIPRILTECGHTICTGCAGKI
                     KGQSSIIACPFDRIETRIWKKDVTRLKKNFSILEIKQEVKDRKNRVISEKNEKKERNK
                     NGVCDENTNHHASNYCETCDADLCEECWTWIHSISTLAHHEKKMISTPDCQFHPGKSI
                     SLVCMRDRCKKRQNRLMCSECFLDKCSDHFEHEHSSLHLELPELRRNICSSLALYHEK
                     EKKILANIGKLRESVYTFFQYQYLYISTVVVL"
gene                 complement(join(12592..12935,12979..13146,13199..13306,
                     13353..13383))
                     /gene="ZK945.6"
CDS                  complement(join(12592..12935,12979..13146,13199..13306,
                     13353..13383))
                     /gene="ZK945.6"
                     /codon_start=1
                     /protein_id="CAA88439.1"
                     /db_xref="GI:3881890"
                     /db_xref="SWISS-PROT:Q09382"
                     /translation="MECSQEDVVNDFIALEKIGSEVDINLDGVIKSKECSNTNEADII
                     SNLITAIEESLSCTSVCTAVSLETVAQKLDAYADPSLNTQMSFSTASDLSSMEQDYVK
                     ASDDPFDLNHQPSPLQVWRDQGKITGFQMMCDDQKVTVVDSLECLAQSEQHLEPVYFD
                     PRVNLAIPCPPDDFEILEDYGSTSNASVNSDDASTAELGPTSEEFEEWVRKIEQNY"
gene                 complement(join(14003..14067,14111..14488,14536..14703,
                     14747..14885))
                     /gene="ZK945.7"
CDS                  complement(join(14003..14067,14111..14488,14536..14703,
                     14747..14885))
                     /gene="ZK945.7"
                     /note="cDNA EST EMBL:AW057403 comes from this gene
                     cDNA EST EMBL:AW057480 comes from this gene"
                     /codon_start=1
                     /protein_id="CAA88440.1"
                     /db_xref="GI:3881891"
                     /db_xref="SWISS-PROT:Q09383"
                     /translation="MASSFDNQMDQDGMCSVYSAQPSETNCSINEVLAKEIIAVNETP
                     DDQADSSIYPIPKSETNVSASEGFQPCQDINQFNLSVYSAPKSETPVTMNEKFERCKD
                     LMNVLDYSVYSMPPSEANVTMNVASFSEYTALASETNVTMADVLKNVAQDLASEHTAK
                     SAHPTFDTTAYVERLQAELGIPDSKVIGLECSNFSNAKIIDSIECLHQLDKFQPIPVD
                     FDQNPDFGKTAKSVESYLLRSSNASSIHHEI"
gene                 join(15183..15300,15348..15559)
                     /gene="ZK945.8"
CDS                  join(15183..15300,15348..15559)
                     /gene="ZK945.8"
                     /codon_start=1
                     /protein_id="CAA88441.1"
                     /db_xref="GI:3881892"
                     /db_xref="SWISS-PROT:Q09384"
                     /translation="MQAPVVTETCQTNEEGEQLVLRLRAPVERPRVTWGAGVIDNEHM
```

GRLKSNCCCIYTPPRVWDDPSTWEPEEHETEHCRGHTLPEKKQKPQGGHGSDKDEDKG
NCGCDHC"

gene join(complement(Z48582.1:379..564),
complement(Z48582.1:145..330),complement(27844..27976),
complement(27442..27582),complement(27257..27396),
complement(26887..27211),complement(26027..26658),
complement(25897..25975),complement(25195..25742),
complement(25071..25149),complement(24444..25021),
complement(24316..24394),complement(23589..23756),
complement(22533..23545),complement(22407..22487),
complement(22064..22357),complement(21765..22014),
complement(21491..21717),complement(20608..20835),
complement(20457..20558),complement(20142..20410),
complement(19095..20087),complement(17988..18853),
complement(17735..17940),complement(17394..17689),
complement(16802..17350),complement(16384..16758),
complement(16088..16331),complement(15760..16029))
/gene="ZK945.9"

CDS join(complement(Z48582.1:379..564),
complement(Z48582.1:145..330),complement(27844..27976),
complement(27442..27582),complement(27257..27396),
complement(26887..27211),complement(26027..26658),
complement(25897..25975),complement(25195..25742),
complement(25071..25149),complement(24444..25021),
complement(24316..24394),complement(23589..23756),
complement(22533..23545),complement(22407..22487),
complement(22064..22357),complement(21765..22014),
complement(21491..21717),complement(20608..20835),
complement(20457..20558),complement(20142..20410),
complement(19095..20087),complement(17988..18853),
complement(17735..17940),complement(17394..17689),
complement(16802..17350),complement(16384..16758),
complement(16088..16331),complement(15760..16029))
/gene="ZK945.9"
/note="N-terminus contains five repeated domains and the
C-terminus shows similarity to the polycistic kidney
disease protein 1 (PIR accession number A44604), contains
similarity to Pfam domain: PF01477 (PLAT/LH2 domain),
Score=130.4, E-value=1.1e-35, N=1; PF01825
(Latrophilin/CL-1-like GPS domain), Score=62.0,
E-value=4.1e-15, N=1
cDNA EST yk155e4.5 comes from this gene"
/codon_start=1
/protein_id="CAB70192.1"
/db_xref="GI:9665271"
/translation="MVLRFSPPFRFSTTSFFSCCLFCSEFIFVFRRIFTKLLQDNLPA
HWMKKSNFFVLLLLAISAIQIDGLHYQLLDGIATFRLDNDDTTIGGVPRNSQGVVKIK
LSCGLNRLSVENKVTEVSSLELIHNCIQTETRLVGLFLNSTWITLNEVNDDDEISIAV
EAKYEVCYDDGIDRCDGSLWWLQVGGNEMALLGYREKCESGEINEEYARRMCKRPYRS
EKSTAISDSQGVYYDGQVLKGVRAKQFSMRTSGSPTLRRMKRDAGDNTCDYTIESTST
STTTPTTTTVTSTVTSTTTVPTSTSTVTTAMSTSTSTPSTSTTIESTSTTFTSTASTS
TSSTSTTQQSSSTITSSPSSTTLSTSIPTTTTPEITSTLSSLPDNAICSYLDETTTST
TFTTTMLTSTTTEEPSTSTTTTEVTSTSSTVTTTEPTTTLTTSTASTSTTEPSTSTVT
TSPSTSPVTSTVTSSSSSSTTVTTPTSTESTSTSPSSTVTTSTTAPSTSTTGPSSSSS
TPSSTASSSVSSTASSTQSSTSTQQSSTTTKSETTTSSDGTNPDFYFVEKATTTFYDS
TSVNLTLNSGLGIIGYQTSIECTSPTSSNYVSTTKDGACFTKSVSMPRLGGTYPASTF
VGPGNYTFRATMTTDDKKVYYTYANVYIQEYSSTTIESESSTSAVASSTSSTPSTPSS
TLSTSTVTEPSSTRSSDSTTTSAGSTTTLQESTTTSEESTTDSSTTTISDTSTTSSSP
SSTTADSTSTLSVDQFDFILDSGLSWNETRHNEDSINIVPLPTNAITPTERSQTFECR
NVSTEPFLIIKESTCLNYSNTVLNATYSSNIPIQPIETFLVGIGTYEFRINMTDLTTM
QVVSHIFTLNVVADSTSTSEVTSTTSTGSSSESSAISTTSGIESTSTLEASTTDASQD
SSTSTSDSGTTSDSTTIDSSNSTPSTSDSSGLSQTPSDSSSASDSMRTTTVDPDASTE
TPYDFVLENLTWNETVYYSENPFYITPIPNKEPGALTTAMTCQCRNDSSQPFVLLKES
NCLTEFGKNGAYSASVSFNPMTSFVPATGTYEFLINVTNRASGESASHIFTMNVVLPT

TTTETPPTTVSSSDDAGGKTGGTGATGGTGGTGSGGSATTLSTGDAVRSTTSGSGSGQ -
SSTGSGAGGSGTTASGSGSGGSSGTGSDGVNSGKTTALNGDGTGSGTATTPGSHLGDG - -
GSTSGSGSDSNGSSGVSTKSSSGSDTSGSSDSSGANGAFSATAQPSTRTTKTRSSLAT
VSPISAAEQAIIDAQKADVMNQLAGIMDGSASNNSLNTSSSLLNQISSLPAADLVEVA
QSLLSNTLKIPGVGNMSSVDVLKTLQDNIATTNSELADEMAKVITKLANVNMTSAQSL
NSVLSSLDLALKGSTVYTLGVSSTKSKDGTYAVIFGYVIASGYTLVSPRCTLSIYGST
IYLTGDTRASYKQLDGDTVTADTMLAAAIGIQGMFATNGRTVQVEQDKIDDKRSLVSG
NIMATMSGVGDVQSGEYSYNDMYVTAWNVTYDNSTVGSTSQKNTSFSFNIPVSEVQYI
LLIESGTMIKLHSTQNIVSRGLVVTASYGGVTYTITCTNGTGKFVEVDTDNAIFSYNA
DSFTVVASDGSSASTVKKLIQMPIVIENVNLALFNQTTSPLVFSNAGSYSMRMVLSPQ
DIGIPAVSALSQTVSISTLSPTASYTKDDLQSLIKEQTLVTVSGTTSNSLLSIAGSLT
SALKIALDNPLSSDLAANLKYATDNYDSLYNVLPSDPDNIVYVEEMTSEEWAAYVTKM
FQKNIAKNLANQLASTLDTLENTLAARAIATGNLPYDYSNSVDGTGMVIVIDDASNIV
GKTQNCEEWAFKLPSPASTLNTAEITDKTLIQVGLVCYATNPRTYVDNFDMLITSGAL
EAHIKDENQIIIPITGTTAPIYVNGRGSEDDAVLTLMQQGDFASYQILDLHAFRTTNW
NNSLQVEIIASQDYEIPNNDDTYMFSSFQSLPGPLESNHEWIFDLNTLNKTSNYFVTA
GNLINNTGLFFIGIGKRNSSTNTGNSSDIVNYGQYDSMQWSFARSVPMDYQVAAVSKG
CYFYQKTSDVFNSEGMYPSDGQGMQFVNCSTDHLTMFSVGAFNPTIDADFSYNYNVNE
IEKNVKVMIAAVFMLVVYGCLTINAIICQRKDASRGRLRFLKDNEPHDGYMYVIAVET
GYRMFATTDSTICFNLSGNEGDQIFRSFRSEEDGNWEFPFSWGTTDRFVMTTAFPLGE
LEYMRLWLDDAGLDHRESWYCNRIIVKDLQTQDIYYFPFNNWLGTKNGDGETERLARV
EYKRRFLDESMSMHMLAQTISWFAMFTGGGNRLRDRVSRQDYSVSIIFSLVVVSMISI
TILKSDNSIISDSKSVSEFTFTIKDIAFGVGFGVLITFLNSLHILLCTKCRSHSEHYY
YKKRKREDPEFKDNSGSWPMFMAGMARTIIVFPVLMGLIYISGAGMSLMDDLANSFYI
RFLISLILWAVVFEPIKGLIWAFLILKTRKSHKIINKLEEALLRAKPAETFLRNPYGK
IEKGLGTEIADVTKLRDTENRKMRDEQLFITIRDMLCFFASLYIMVMLTYYCKDRHGY
WYQLEMSTILNINQKNYGDNTFMSIQHADDFWDWARESLATALLASWYDGNPAYGMRA
YMNDKVSRSMGIGTIRQVRTKKSAECTMFKQFQGYINDCGEELTSKNEEKTLYMQAGW
TELESENGTDASDEYTYKTSEELSTETVSGLLYSYSGGGYTISMSGTQAEIITLFNKL
DSERWIDDHTRAVIIEFSAYNAQINYFSVVQLLVEIPKSGIYLPNSWVESVRLIKSEG
SDGTVVKYYEMLYIFFSVLIFVKEIVFYLYGRYKVITTMKPTRNPFKIVYQLALGNFS
PWNFMDLIVGALAVASVLAYTIRQRTTNRAMEDFNANNGNSYINLTEQRNWEIVFSYC
LAGAVFFTSCKMIRILRFNRRIGVLAATLDNALGAIVSFGIAFLFFSMTFNSVLYAVL
GNKMGGYRSLMATFQTALAGMLGKLDVTSIQPISQFAFVVIMLYMIAGSKLVLQLYVT
IIMFEFEEIRNDSEKQTNDYEIIDHIKYKTKRRLGLLEPKDFAPVSIADTQKDFRLFH
SAVAKVNLLHHRATRMLQTQGQYQNQTVINYTLSYDPVSAIHETGPKRFQKWRLNDVE
KD"

BASE COUNT 8528 a 5366 c 5484 g 8603 t
ORIGIN

```
      1 gatccctaca aaaatttat tcgaatatgt tctaattgct taaagttttc tttattcgaa
     61 aattattcaa tttttgaaga agatgtttga aataatgttt ttgcaatttt attttaaact
    121 cacaaaaact acagtaaccc gttcctatcg ctagtagata aatgtttttg aattagaacg
    181 aaaaattcaa tttccggttt tttcgcggtt ttcgtgagaa aataagaaat gaaagagaag
    241 gcaataaatt ccaaaggtcc agattcaatt tcgcccgcgc gttttttctc tcagtctaat
    301 gagcttaaca tatgtaaatg agctacgaaa ttgatggctc ttcatgagaa taggcttgga
    361 ttagaaattg aagattaggt ttgtcttgga gggggactcg aaaaacggtc aacggttcac
    421 attgattttt actattaagc atctatgtat gtgtagtcat tttggtaaac ccataacagg
    481 cttggtgtac ggaagtatga tgtcaaggta ttaatttgat aacttgtcaa actagtttag
    541 tatgtataaa attttcaatt tacttttata aattaaacaa acaacgcaaa atacatctgg
    601 attgaaacag ttttctgtca tgaaaagcaa acatttacaa aggtttacaa tgcaactact
    661 aaatgtttac gaagatttta tgaaaaacgt taatcttgaa cggattttga atattctagc
    721 cttcaattac tttagacatt ttacagcaga tatcttatac cagtaaacta atgacacttt
    781 tcaaattaat cattctaact acgttcgtaa ctattcccat ttcatgtttc acctttgtac
    841 tatgttgtat gattcagctg ataagctcct ctctaacttt tgctttacct ccttctcctc
    901 ctccttattt ccttgactat atgtctctct tatcacattt ctgctcgttg ctctggtttc
    961 tttaaatttg gctccactca cttcaaataa atttttgtcg tgtttgtaaa catttccata
   1021 ttttttggtg gagttttcaa atatctcact gtatttaatt tctttatctt gaagctcaca
   1081 aaccaccctg tctgtctgtt tgtctgtttg taggttttca gtgaaacaac ataaccaact
   1141 aaccacaaat acacatattt acacatataa tattcctttg caactggttt ttcggatata
   1201 atataattgg aatggactgt tgactctctt ccccttcacc ctaccacctt ttctctttta
   1261 ttttccccta acttttcccc atttaccaca acaactacgt cggattatga aaactaaaag
   1321 tgtttcattc aatttaatat tgttattttc aaagtgatgg atgcgatgga ggacaagggg
   1381 gagaccgagg cggaaaacgt tgtcaaactg gaaacgggtt cgtcacggcg cctgttgatc
   1441 tacggaatcg ccaggtgagt ctcactttca cacgttttag cgctccttac cttaaaaatt
```

```
1501 tacacatcgg tcggtggtcg tgacaaattg ttcagttttg atttcaatct tatgatgaga
1561 tggtgaagct tgaaaattag agattgaaga ataaatcatc taccaagttt tctcaatttt
1621 tacagcttat gtcctggttc ttttgatttt atcccaaaat tgtcaaatgg caacaaatgt
1681 attgtttatt tttctattga aagttttgta aattaatcaa aatgagcaga gatacgagct
1741 gtcaaagtag aatagcaaat tatttcttcg cctgaaacat tgctccacat tctttttttt
1801 ctcaaattta tgttcaccaa ctcgaaccca cacttcactt ctgtgcactt tgctgaaaca
1861 tatagcatag ttagaaggac atcgttatca gtaaaatcac atcagctgat aacaaagaaa
1921 ttaccaatat gtcaatcatc tatcggcttc ttttcttttt tgttaataat ttagtggttg
1981 aaactatatg ttggttgtat tataggaatg ggtgaactgt gaaaattgag gtatgaagaa
2041 gcattttgaa tttttagagg ctcaaccatg atttagatct tctgcaaaag cccatcatat
2101 tctatgaatt tgaaaatttc caaaactttg aataaaactt cccaaatttc caaaccattc
2161 tacagtgttt tatcatgaat cttgactata ttggattata ataactgttt ttgccgaaat
2221 ccctatcgaa tctatttcac tgtcattatc cctaaataat tccttcaaaa cttccttacc
2281 cctattcaaa aaaagaaatt aaaatcagat gttttctaat ttctacccat cataaacgca
2341 ctaaaattga agatatgatt agttgactga agattgacta attggtcaac aatacatttc
2401 atttggcctt cgtcgtttat ttcttgtttc cagtctcttt tgcaatgtat tgttctactt
2461 ctttcttctc tctgaaattg tgaaaacata aaataaaatt caccacaata gccattcaac
2521 ctccttctgc ccgtgtcaaa tatctagaac ataatgacct cgagaaacta gtcaccggct
2581 tcttcctctc tcacgcactt ttccagtata tacaaatatt tacagtattc tcgcagtttc
2641 cggggcgtgg cttgtcgtgg caaccaccgt cgacagtctt gcgtgcttca ttgaaggcga
2701 aatgcatctc gacaacttgg ttggacatgt ggcacctggc tacgagaagg tggaaaaagt
2761 tttcaggtga gtactgtttt gaacttaaga attctgctac gtctattcga aggcaatgta
2821 ggtaatctcc aaggtgaact tcttggtaac actgacgtgt aggcaggtag gcatgtaggc
2881 aggcaactta gagccaccaa aatagttctg caaaaattgt caatttttct gccaactttt
2941 tggtatctac aagtaagtat taattgtaga ggtatagaaa aatgttttaa tgattttgag
3001 atttgttata tctttccaga aaaataaaca ttatttttta aatcactaaa atatttgttc
3061 tatatttctg catatttggt gatattttta gatactttct aaaaattttc agcgcacctt
3121 tggactcgac tccatgaatt tcatagaatc caatttttgt gactgatctc tagaagcgtc
3181 ttttagaaac atttccctat gactataaac tacactttct tcctgacaag gtcatacatc
3241 tcactctctt ttccaccaaa ttatcctcca ccatcttgcg tctttttttgc aaagaaagtg
3301 agaagcaaag tgaacagtgt aaacaaaaag ctattcattc acaattcaat tcaaaaacca
3361 attcttcttc aattcaatgc cacccttctt tcgatttcag acgaaacttt gccgatggtt
3421 gggaacgtga gggtgcgtcg attaccgtat accacaagga tcgggtgatt gtggatcttc
3481 aaggcgggta tgcggacaag gcgtcgggca ggaaatggac ccctgacacg agaacagtcg
3541 tgttcagtac aacgaaagct gttggagcag tctgtgtggc aatgttggtt gatcgaggtc
3601 acatcagtta tgatgacaag atgagcaaga tctggccaga gtttgcacaa aatgggaagg
3661 agaatatcac aatcgattgg ttaatgtcac acagagtatg tttaatcttt ttggtttcta
3721 aatctaactc gaggtccaaa aaattcttag gcagcgctgc ctaagaattg ccggcatcaa
3781 taattagaaa cgtttgaagt taaggttttg ccgctaatgc ctaacgagac ccagcttttg
3841 ggagaggagc gttataattt agccttggag cgcaattcca cctcgattta aaacatgcat
3901 ttttctgcgt ctccataata tatggaaaac tgtgagctca ctccaaagga actcattttt
3961 taaaagctct tttctagtgg aaacgagaca ataggtgcta aattttcaat tgtaaatcct
4021 ggttttctct gtgcacttta aaattcgaaa ctttatcaac tacattttca atatgaaacg
4081 aaaaaatttg ttaaatttgg agcctgtagc ggttactgta actgagatcg tggcgagacc
4141 caatgggaaa aaggcggcgc cagaaaatcg caatgcaata ataaattata aaaattcgca
4201 tgctgaatca cattcaagta aattcttaat tccaggcagg tcttgctgca ctcgatatgc
4261 caataaccat cgaagacgcc aacgatttcg agaaaatgag tgaagtcatc gcatcacaaa
4321 aaccaaactg ggaacctgga actaaatctg gatatcatgc aattacttac ggatggatcg
4381 ttgatcaaat cgttcgacgc tccgatccga aaggtcgatc agttggacga ttcttcaaag
4441 aagaagtcgc cgatgttcac ggaatcgact ttcatattgg attaccgcca agcgaagagc
4501 ataccgtatc ccgtctttca atgccgtcca cacttcatct cgttcgggag attgttcatg
4561 atccacgtgt tctgattgta cttgcagttt ttaatcttcg accaccaaat tctattgcaa
4621 gaaagattgc tgcaaatcca acgtggttca agttggaaca ggatgtgaac acctttaata
4681 atccaactct acatgctatg gagcaagtcg ctgctcttgg tattacaaag tcaagagatt
4741 tagctagact tttctcactc gtacaacaag gaaaactgtt ctctactgaa cttctagaaa
4801 agttccgtgc cccccaagtt caggggattg atgaagttgt catgactcct ctaccaaaag
4861 gacatggttt cctatacgag agacatccaa tgggaggggt gagcatcgtt ttaataaata
4921 taataataaa tcaattattt tttcagaaaa agtggcttgt tggacatcct ggttacggtg
4981 gcagcacagt aatgatggat ttggaagatg ggatcacgat tgcctacgtc tcgaatggat
5041 tgaaaactgg aatgggagag cttacgagaa catacagaca tcttcgagat tctgtatttg
5101 agtgcttgga gaaacagaag actggtcaaa gtgtgatgat cgaggaagca gttcaagcag
5161 ttgccgcata acttaaaaaa ttgttgttat ccttgtttgt acatagcgcc ataatttggg
5221 acgggtctac tgcccccagc gaattgtgca taaacatgtt tctggtttgt ctgaatttgt
5281 attgagaaaa atgggtaata ccgggaaacc gaaaaataat gaacagaaaa agttaaaaaa
```

```
5341 aaacatccgg gtgcaaaaag ttcttcttga agtcggtgag tcggtttgaa gtacaataaa
5401 atgactcgcc gagcgcaaga agtttaccag ggcagaaaga agagagctga taataaatta
5461 aaaatgtgaa taaatacacg agaatgattc aatcgtccat gtcgtcctcg tcaagcttgc
5521 aatagcccat tcctcggcag cagtgacaac ctcgcttgga acttcttcgt actttccgtt
5581 cgtctgctca ccgacccatc ccatttcgat ttgaacgttt ttatccttgt tctcgtcacg
5641 caccaccata atgattcgag cagcttcctt cacgagttga ttcacatcca gctcctcgat
5701 cttcagcttc tcaatctcag cttttgcggc ttggcgatgt tttccgacag cccatgcctt
5761 gtattcatag tttagacctg atggctccac aaggaaaaga cgtcctccag tttgtttgtt
5821 ccatgacatg aagaaggctc ctgctccaaa cggacgacta atgccgagag tgtgaatgtg
5881 aatgtactca gcaactgagt tagcaatatt ctgaatcggc attggctcac ggtagtcttt
5941 gagccacttc attgcttctc cgtaagcata gttcttcaga gcgaaaccat ctggatagtt
6001 tccagcaact gcgacaccaa cattgtcgtt cacgttaaac attcttggat tagcgttctg
6061 aaaattatag ataaaatctt gaaaatctct taaattactc acatcagtgt aaagtttgga
6121 agagatcagc ttgtcagcaa cgaccacaac tccgttcttg ccacgaattg caatcattgt
6181 tcctgcattg tcgacagcct tttgagcgta ctcgactgaa aacgagatta tgagtatttt
6241 gaacaaagca aaatcgaaac aaaccttgga aaattctgcc atcaggagaa aaagtagagg
6301 cggcgagatc gtagccggta ccgattgaac tcattctgca aaataaaaac tatgttaaca
6361 catatatgat tgcaactggt acgtgtttta tttctgcgga aatcagaaga accgttaaaa
6421 tttaatattt aataattcgt ttatttgaat gcgttaaaaa tagtagaatt attgcgaaaa
6481 taaaagctga taatctgaaa atggcagcta aatggaaata aaatttcaaa tgatgatttt
6541 ccaatgtcga tttacgggag agacgaacat tgcggcaggt ctcgcaacga cgaagaagag
6601 agtgtgtaaa ttgagagacg tcagaagaca acatgcgcct ttaacatttt cttttcattt
6661 ttctttactt tttcgtaact ttttgttact attttgaagc tgtgcaattt gtttccaaag
6721 taaaaatcgc ttaaacctca cataaaattg tcttgtgttt attactcctt ttaatatgcg
6781 tgtctttcag agaaatctcg cgggtaaaaa tggtgaaact cgacgacaaa aataaaaaat
6841 tcaaagggaa gaagaaggtt aaaaatgtgt tggagaaaaa ggcaaaagga ttaaaactca
6901 acaaagtaga cagaaagcga attgttaagg tttgttaaat tacttcattt tgtaaataat
6961 tttttgtgaa atatttcaga ttgaagaaaa agcagcgtta aaaagcaaag tagacaaagc
7021 tgtgaaggac gagttggaaa ggttgaaaaa gtcatcttca acatcagttt ttgataatga
7081 tgggactcgt gactctttgt gctcggagtc ttcgttcgga agccagccag caccgaaaaa
7141 gaaatcgaaa aaagtgcttt tctcaggaga acttgaacat gttaaggttt tcgataagcg
7201 agttcaggat cttcaaatca aaccatcaga ggcatctcca ggaagaggaa ttctcagatc
7261 ccctcttgat aagaaggtta aggtttgtta attcaatata tcgtctttta cacaattgtt
7321 ttttttcaga aacttgccaa agtgaagact gtcaaagttg ctcaggaaga agaagaagag
7381 cattccgctc ccccaaagaa aaaagtgaag gttaatgcag agaaagccgt tgcttctgag
7441 ccagcagacg atgaaaattt ggaatctgtc gacgaacaag caggtggaga tgaatctcat
7501 attgacattc caactctaaa gagaaagaga gtagctattc aagtcacaaa gtctgttaaa
7561 gaacaattgc tgaatatgcc gagaaaagaa agaaaagcat ttttgaagga gttgaaattg
7621 aagagaaaac ctgaaggagc tcgtgctcaa aaatgcaagg aactttggga aaagatcaga
7681 atgggaaaga cgccaaaagc tgaaaaggat actgcggttc acgagttgta tggtcttgta
7741 aaaggacacg ctgccaagct gatctatgct cacgacacca gcagagttat cgaatgtctt
7801 gttgccactg aaagagaagg aatcattaac aactgtaagt tttttgaagg ttcccatgaa
7861 taattacgag aacataatta ttgcagtgtt caacgaatta accccagaaa tagtgaggat
7921 gtcaaagaac gtctattcca aatttttcgt caagaaaatg ttgaagaatg gaactaaaga
7981 acaacgtgat attatcatta atgcattccg cggacatgct ccaaccctgc tcagaatcaa
8041 acatgctgcc gaagttcttg aatatgctta caatgacttc gctaatgccc atcagcgtta
8101 caacatcatt actgaatttt atggaaaaga attcattttg ttcagagtaa acaacattca
8161 attaagctct aaaaatagtt tgttgatttc aggaagacaa tatcagatct ctgacggaga
8221 ttctcgctga aaagccggaa aagaaggttg tgattttgaa gcatttggac gaggttattg
8281 gagcagtgaa tgaaaaagaa actttgcgac tttcaattct gcacaaactt atgctcgact
8341 ttttcgataa ttgcgacgag gaaaagaaaa tcaatctcct tgattcactg aaagataaaa
8401 ttcccgagtt cattcatact ccagatggtg ccaaattggc tattaaactc atttggtttg
8461 ctccagtcaa ggaaagaaaa ttgatcgtca agaatttcaa ggatttgtca gtaaaagccg
8521 caatggaaca ttacggacat cgtgttcttc ttgcactttt tgatactgtc gacgatactg
8581 ttcttctcaa taaggttatt gtctccgagt tggcaaatga aatgaagaag ttgatcgaag
8641 atgattgggg agagaaagtt atccactatt tggtgcatcc aagagatgga agaggaatcg
8701 acaaaagaga aattacattc cttgccgaag gtgatagcaa tccacactcg aagaaaactc
8761 aaaaggatag atatggacag ttgtacgccg gtattaccga gaacttgtat ccttatttgg
8821 ctgctaactt cgaagagctt gttttcgagg ccaacaagtc aaaattcgtg gctgcatgtc
8881 tcgaaaccac ctgtaagttt aaaagttgca caattataaa gaattcgagt ttttttcagc
8941 aagcttcgat ttgttcgatc gacaagtccc agcagaagct cgcaagagtt gcaaccaagc
9001 gatcgttgaa ttggcgaaga aggactttgt accaatggac caggaaggct tccacattat
9061 tgaacaccaa tcgggcaatt tcattctcat ggcagtcatg cgctgtgatg ccgctctaca
9121 agaagatgaa cgtttgtcag ttgcattggc agaaggactt acgagcaagc agcttggctc
```

```
 9181 gtgggtgact tgcaatcgcg gttgccatgt tctcttgaaa atgcttcaag ttggaggacc
 9241 gaaagttatt gaaaaattga aggcttcgat cagcagaaaa cacttggatg gctataactc
 9301 aaaaggagca aatcttctga aggcacagct cgacggaaat gtcaagaagt gagaatgcaa
 9361 ggtatacgaa ttaatttttg ttgattttat ttgttttgag ggattcgtcc tatacatctc
 9421 taaataccac acctttttat tgttctcgtt attttgttgt tgacttttt tttattactt
 9481 tttgcatctc gttaattttt tgaaacaccg tacggtaata aaaaggaaaa atataaaaaa
 9541 aacgttgtaa aaacacagaa ttgagatcat aataacagtg tgcaattata attttagatt
 9601 attgattcat taacaatttt ctcgatatcc tcgcttcggt cgacatttac gacaacggtg
 9661 atttttggca ttttgttatg gagatccgcc agcttagtga gaaaattcga tgcagcttcg
 9721 ccatgtccac gagaatagct tttcagacca acaattattt tttcatatgc tacagcttct
 9781 tccaactgct ccagagcgac aaagtatcga tcacgatcac catcgagcag atcaactatc
 9841 attattaagc cttaatcttt cagttttcag atgacgcaac aattatcgaa aaactcacgc
 9901 aatccttcag aataaatcgt aagatcttca gttctgtcaa tgatttctaa aaagtcgcaa
 9961 ttataacgaa gaatgtttct gtaaattgaa gaaattgtag aataactaaa taatagactt
10021 acgatcggga cgaaattcga gtgctgtggt tttcgatgaa ctttctcact tcgtttcggt
10081 gacactctga aataagaaaa acggaaattt gttgaatttc cgaaaagaaa tacctcgaat
10141 ttccaatcta aatgccggta tcatctcaat ttgcaatgga cgttgtgata gaacatgaac
10201 aatacacgtc gagcagtcag ccaggaactc tataaaataa attacagatc ttaaactctt
10261 tagataaagc tcaataccag gtcttctgac agctgaatcc ttttcaatcc gcttcacagt
10321 cacttcaagt tcccactttc gctgaacaag cttcatattc ggcagagccg acagtttcac
10381 aatggcatcc ttatttttct gcagccaatc gagatccagc ttctggttgg agattttata
10441 ctcgaggact cggactcttt tcaccacctc gttctccaat actttgattg cttgatccat
10501 ttctcccatt tcaaaatgtc gaaatctcag gagctcattc ttttttgga aaaacggctc
10561 tccgtcgtat gagtatgtgg caattattct gaaatgttat attgataaat catttactat
10621 gtattcataa agctctgtag tttgaacttt actatatgta ctgtagtggt actgtagggt
10681 tactgtagct tcggaataaa ttggtgtttg tgctttttga gaggtattcg gcaggaataa
10741 gttttgctat tactgtcaaa catttatcac atggaaaatt aaaaacaaat aaaatttga
10801 gaatgtaatc tggcttcaaa aaaaattcca gaaacttgga tatttcaaaa tggcaaaatt
10861 caaaataatt acaagttttt gcatattccg aaagaaaaaa gagaaaccaa ctatttacca
10921 accgagtact ttttccaaaa ttcaagtttt tcctggacta cagtaaccct acaataattc
10981 cacagtacag taccactaca gtaactagac attagccatc actaactcca aacccaaaag
11041 gaaaaatacc cattttctta atctacagta accctacaat aattccacag tacctctaca
11101 gtaccactac tgtactaata tataagtatt gatattgaaa aaaggtatac actgactctc
11161 taagttttcc aatattggcc aatatcttct tctctttttc atgatacaat gccaacgacg
11221 aacagatgtt ccttctgagc tccgggagtt ccaagtgtag agagctatgc tcgtgctcga
11281 aatgatccga gcatttgtcc aaaaaacatt cgctgcacat cagtcgattc tgccgtttct
11341 tgcatctgtc tctcatgcac acaagactta tacttttcc tgggtgaaat tgacaatcag
11401 gagttgaaat catcttttc tcatgatgtg ctagtgtgga tatagaatga atccacgtcc
11461 agcatctaaa aatatttatt attttctgat caagatttta aaatgacttc caaaaggcgc
11521 acgggattat ttatatgggt ctcgtcgcgc aaaacgttta tggtagcttc tttgcggccc
11581 tctcgttcat tttcatagtt ttttttaaaa tttattctgg accgcaaaaa ttgaaaaaaa
11641 aactaccata aacttttttct tgcgcgccga gactcatcta aataaatgag tgcgccttta
11701 aaaagccatg tcaaaatctt gtgaaactga taatatttca actaactctt cacataaatc
11761 ggcgtcgcat gtctcacaat aattcgaagc gtgatgattc gtgttctcat cacagactcc
11821 attcttattc ctctcctttt tctcattctt ttccgaaatt actcggttct ttcgatcttt
11881 cacctcttgt ttgatttcca gaatactaaa attcttttg agtctcgtca catcttttt
11941 ccaaattctc gtctcaattc gatcaaatgg gcatgcgatt atcgaagact gtccttttat
12001 ttttcctgca catcctgtac aaatcgtgtg accacattct ggaagataaa ataatttta
12061 attaagaatc aaaacacacg gtgtaccagt caaaattcta gggattagga gcttttcgtc
12121 ttctgaatac tcctgcccgc aaatcccaca ctccggaaag cagcggagca tattcatggc
12181 aagttctgga aacgaagaaa aaatattcga gtgtatgaaa tgaatgggaa atttcgttat
12241 tgtcgttgtt gaaaacgaaa atgttcgttt aaaatacgaa aaacgaatac gaaacaagaa
12301 acagcgcgat gacaccaatt gaccacaaat ttgtgtaaat ttggagcaat ttccggagat
12361 caaacagaga aagaaaacac tttgaatatt cttgatatgc agagagtgtt cgaaaactag
12421 aaaaagagag cgcgaggaac aaaagtagaa agagtataat gtgcacacgc gaggcgacag
12481 ggggcctagg cagttgttgt tttcaactcg ttttagactt tggagacgca gagtcagata
12541 tgcaaaacta ttatcttcaa tgagaaaaaa tgtattttat caaatagcta ttcaatagtt
12601 ctgttcaatt ttccgaaccc attcttcaaa ctcttcagac gtcggaccaa gttctgcggt
12661 tgaagcgtca tccgaattga ctgatgcatt ggatgttgaa ccatagtctt caagaatctc
12721 aaaatcatct ggcgggcacg gaatagcaag gttgacacgt ggatcgaagt aaactggttc
12781 caaatgttgc tccgattgag ctaagcactc cagagaatca actacagtaa ccttctgatc
12841 atcacacatc atttgaaatc cggtgatttt gccttgatca cgccagactt ggagcggcga
12901 cggttgatga ttgaggtcga aaggatcatc tgaagctgaa aataaatttt ttaaaattta
12961 attgagacgg aatcccacct ttaacataat cttgttccat agaactcaaa tccgatgctg
```

```
13021 tactgaaaga catctgagta ttcaaagaag gatctgcata ggcatccaac ttttgtgcca
13081 ctgtctccaa tgatacagct gtgcagaccg atgtacaact caaagattct tcgattgcgg
13141 ttatcactga aaaatctggt gattcaagat catctgaaat cgtttaaagg caactcacag
13201 ttactaataa tatctgcttc gttcgtgtta ctacactcct tgcttttgat gactccatcc
13261 aaattgatat ccacttctga accaatcttt tcgagagcaa tgaaatctga aattctacgg
13321 ttcagacggc atgacaaact cagtaaaatt accattgacg acatcttcct gagaacactc
13381 catgattatg atctctcgag atgtgatcga tttgaaaatt tttttgaaat gaaattttga
13441 atataagaaa atgaacattg aggcattagt aggaaagacg tgaaaacatt taattttata
13501 aaaatttaaa gaacacggtt gccacgtgat tggtgaaaac ttgtacaaag aatttataga
13561 tgctcacaga ggcaactcct ttcgaacagt tctctcaaaa agtaggaaat aatggaaatt
13621 gagaagaagc accacatttt atgtacagtt aacattaaat agcatggtag aagtaactta
13681 gaaccacgag gctggtagat cgcaacaagg gcgggtgaag aattgatgca aatttcagat
13741 ttatagggat aagacaactc tttttagaag aattcccgtc ttgttaggtg ttcaacccgg
13801 gagccatgac ggggctcatt ttgtccgcct cgctttcatg tgtgcaaaag gcggccaggc
13861 acaagtctcg tttccatgaa ctatcgtaat agtcatcaaa aaatttgcta tacaaaaaac
13921 caagaaatta cgaatgcata gacaacaaca aaaatgattc gacatttttt atagaccaag
13981 ttcaataatt tgttccgatt cttcagatct cgtgatggat tgaactggca ttggatgaac
14041 gcaagaggta gctttccaca gatttggctg aaattgaaaa tattatttct taaataaact
14101 tcactcttac cagtttttcc aaaatcagga ttctgatcga aatccaccgg gattggttgg
14161 aatttgtcca actgatgaag gcattcaatt gaatcaatga tcttcgcatt cgaaaaattg
14221 ctgcactcca atccaatcac tttgctatcc ggaatcccga gctcggcttg aaggcgctct
14281 acgtaggcgg tggtgtcgaa tgttggatga gctgattttg cagtgtgctc tgacgccaaa
14341 tcctgagcaa cgttcttgag aacatcagcc attgtgacgt tggtctccga ggcaagggca
14401 gtgtactccg agaagcttgc aacattcatt gtaacatttg cttctgatgg tggcattgag
14461 tagacagagt agtcaagaac gttcatcact gaaaattttt ggtttttcaa gatagagttg
14521 ttgcagttaa cttacagtct ttgcaccgct cgaacttctc attcatggtc actggggtct
14581 cggattttgg agcagagtaa acggacaaat tgaattgatt gatatcttga catggctgga
14641 acccttcgct agctgacaca tttgtttctg attttgggat tgggtagatc gaagaatcag
14701 cttctgtaaa ctcaatattc ccaaaaaaaa gacaataaaa acttacgatc atctggcgtc
14761 tcattgacag cgataatttc tttggcaagc acctcattga tggagcaatt tgtctccgat
14821 ggctgagcag agtacacgga gcacattcca tcctgatcca tttggttgtc gaacgaggaa
14881 gccatagcta accaatcaat tgagcagatt gtttaatccg acggttgagg ttgtcggacg
14941 agtatgtagc aataaattgt tagtgtggca agggggaggt aaggggaatt caaaagttca
15001 cgttaaaagt tcaatttttt ttttgaaatt tataaatttt tttgaaattt gaacttttta
15061 tagtggaatc atggcatttt aaatatatat aaattgtcaa ataaataaaa gtgtaagtcc
15121 acgattccag ggaaaaaatt caaagtttta ttcatttcgt acatcaacta cacagtcgta
15181 cgatgcaagc ccccgtcgta acggaaactt gtcaaaccaa cgaagaagga gagcagcttg
15241 tgctccgcct gagagctcca gttgagcgtc cacgtgtcac ttggggagcg ggagtaattg
15301 gtgagtgaat ttatattaaa aagtcttgaa aaatacttaa actttagata acgaacacat
15361 gggacgtctc aaatccaatt gctgttgcat ctacactccg cctcgtgtct gggatgatcc
15421 gtcaacttgg gagccggagg agcatgagac ggagcactgt cgtggacata ctcttccaga
15481 gaagaagcaa aagccacaag gaggacatgg tagcgataaa gatgaagata agggaaattg
15541 tggatgtgat cattgttgaa actcgaagat ttaaaaatta ttaggaaatt tatgtagatt
15601 ttattgtaaa ttaatctaaa tgacccatca tgcctttgtt cttatgtttt tgtattgaat
15661 attacttttc tgcggtcata aaaatgaaaa aaaaactgaa aaacaaacta ttaacacaat
15721 tatttattct tgatatccaa attaggtagc cctcaaaaat caatctttct ccacatcgtt
15781 tagccgccac ttctggaatc tctttggtcc agtttcgtga atagcagaga caggatcata
15841 ggagagtgtg tagttgatga ctgtttggtt ttggtattga ccttgagttt ggagcattct
15901 ggtggcacga tgatgaagca gattgacttt ggcaacagcg ctgtggaata gacggaagtc
15961 tttttgagtg tcagcaattg aaactggagc aaaatctttt ggttcaagaa gacccaagcg
16021 acgttttgtc tgaaattaaa taacagaaat taaagaacat ctaatagtga gcttgaaaaa
16081 taaatacctt gtattttatg tgatcgatta tttcgtaatc attggtctgc ttctcactgt
16141 cattacgaat ttcctcgaac tcgaacataa ttatagtgac gtaaagttgc aggacgagct
16201 ttgatccggc aatcatataa agcatgatca caacaaacgc aaattgagaa atcggttgaa
16261 tagaggtaac atcaagtttt ccaagcattc cagccaatgc tgtttgaaag gtagccatta
16321 agctccgata tctggaacca atttttaaaa attgatttct ttcaattaag ttttcatcct
16381 caccctccca ttttatttcc taaaactgcg tacaatacag agttgaatgt catgctgaag
16441 aacaggaaag caattccaaa tgacacaata gctccgagag cgttatccag tgtagccgct
16501 aatactccaa ttcttctgtt gaatctcaag attcgaatca ttttacaaga agtgaagaat
16561 acggctccgg caagacaata actgaataca atctcccaat ttctctgttc agtcaaatta
16621 atgtacgaat ttccattgtt tgcattgaaa tcttccattg ctctatttgt ggttcgttgg
16681 cggatggtgt aggctaggac cgatgcaaca gcgagagctc caactatcaa gtccatgaag
16741 ttccatggtg agaagtttct ataaaatgtc ttttgaaac tgaagttctc attagaccca
16801 ccccagtgcc agctgataca caattttgaa tggatttctc gttggtttca ttgttgttat
```

```
16861 caccttgtac cgcccataca agtagaacac aatctctttt acaaatatga gaactgagaa
16921 aaagatgtaa agcatctcat aatacttgac cacagttcca tcgcttccct ctgatttgat
16981 aagtcttact gattcaaccc aactattagg aagataaatt cctgactttg gaatctccac
17041 caacaactgt accaccgaaa agtagttgat ttgagcattg tatgcagaga actcaatgat
17101 gactgctcga gtatgatcat cgatccatcg ttccgaatca agtttattga agagagtgat
17161 gatttccgct tgggtaccag acatactgat agtatatcca cctcctgaat agctatacag
17221 taggcctgaa actgtttcag tggataattc ttcagaagtc ttgtaggtgt attcatctga
17281 agcatctgtt ccattctcgg attccagttc ggtccaacca gcttgcatgt acaaagtttt
17341 ttcttcgttt ctgaaacctc tctattagtt ggaaattgaa gatttttact cacttgcttg
17401 tcaactcctc tccacaatca ttgatgtatc cttgaaactg cttgaacatc gtacactctg
17461 cacttttctt tgtccgaacc tgccgtatcg tacctattcc catacttctt gaaactttat
17521 cattcatgta ggctctcatc ccgtatgcag gatttccgtc gtaccaagaa gccaaaagag
17581 cagtggccag agattcacga gcccaatccc agaaatcgtc agcatgttgg attgacatga
17641 aagtattgtc accgtagttc ttttgattga tgttcaagat tgtgctcatc tgaaaataat
17701 aagttcatct aaatctatgt gcattaaagt ctacctccaa ctgataccaa tatccatgcc
17761 ggtctttgca atagtatgtc agcataacca taatatacaa agaagcaaag aaacaaagca
17821 tatcacgaat ggttataaat aactgttcat ctctcatttt tcggttttca gtgtctcgga
17881 gctttgtaac atcagcaatt tcggttccca gacctttttc gattttccca tagggatttc
17941 ctgaatttca gtaatgaatt ctgatagctt ctttttataa aacttactca agaacgtctc
18001 agctggctta gctcttagca atgcttcctc caacttgtta atgattttat gactctttct
18061 ggttttcaaa attaaaaacg cccaaatcaa tcccttaatt ggctcgaaca ccactgccca
18121 tagaatcaga ctgatcagaa atcggatata gaaagagttg gctaaatcat ccatcaagct
18181 cattccagct ccagaaatat aaataagacc catgagaact ggaaatacta tgatggtacg
18241 tgccatccca gccatgaaca tcggccatga accactatta tccttgaatt ccggatcctc
18301 tctctttcgt tttttgtagt agtaatgttc actgtgggaa cgacatttgg tgcataataa
18361 aatgtgcaat gagttgagga aagtgataag aacaccgaat ccaactccga atgcaatatc
18421 ttttatagtg aaagtgaact cggagacact cttcgaatca ctgataatcg aattatcgct
18481 cttcagaatt gtgatgctaa tcatgctgac cacaacaagt gagaagatga tactgacaga
18541 atagtcttgc cttgacactc gatccctcaa ccgattgcct ccaccagtaa acatggcaaa
18601 ccaggaaatt gtttgagcca gcatatgcat actcattgac tcatccaaaa accttcgctt
18661 atactccact cgcgctagtc tttcagtctc tccgtctccg tttttagttc caagccaatt
18721 gttgaaaggg aagtagtaga tatcctgagt ctgtagatct ttcacaatta ttcgattgca
18781 ataccacgac tctcggtgat ctagaccagc atcgtcaagc cagagtctca tgtattccaa
18841 ctcgccaaga gggctgaaat attaaatttg gtaaatgatt tttgatttga aaacttgaat
18901 tagtccatca aaaaccaaaa caagttaggg ggataaaaaa aactacacgt ccaatctata
18961 attagctcaa ctcacacttg aaccaatcag cgttgtccga atttgcataa ttggttgaaa
19021 cgtgtgtgga gctaatcggt attatttatt ttaattattt ttttattgct aaaaatcagc
19081 gtcttctaac ttacaatgcc gttgtcatca caaatcgatc agtggttccc catgaaaacg
19141 gaaactccca attaccatct tcttctgatc tgaacgatcg gaaaatctga tccccttcat
19201 ttccagataa attgaaacat atcgtactat ccgtagttgc aaacattcga tatccagtct
19261 ccacggcaat cacatacatg tatccatcat gaggctcatt gtctttcaga aaacgaagtc
19321 tcccgcgtga tgcatcttta cgttgacaga tgattgcatt gatggtaaga catccgtaaa
19381 ctactagcat gaaaacagcg gcaatcatca ctttcacatt cttttcgatt tcattcacat
19441 tataattgta agagaaatct gcatcaatag ttggattgaa tgcaccaaca gagaacattg
19501 ttaaatgatc agttgaacaa ttaacgaact gcattccttg tccatcactt ggatacattc
19561 cttcagaatt gaagacatcc gatgttttct gatagaagta acatccttta ctcactgcag
19621 cgacttgata atccattggt acacttcgtg caaatgacca ctgcattgaa tcgtactgac
19681 catagtttac aatatccgaa ctatttccag tgttagtaga gctatttctt tttccaattc
19741 caataaagaa aagtccagtg ttgttgatca aatttccggc ggtgacaaaa taattgcttg
19801 tcttgttcaa tgtgttcaag tcaaagatcc attcatgatt tgattcaagt gggccaggaa
19861 gactttggaa tgatgagaac atgtaggtgt catcgttgtt tggaatttca tagtcttgag
19921 atgcaataat ctctacttga agcgagttgt tccagttagt ggttcgaaaa gcatgaagat
19981 ctaatatctg ataactggca aagtctcctt gttgcattaa agttagcact gcatcatcct
20041 cacttccccc gccgttcaca taaattggag cagtagttcc ggttattcta aaaacatttt
20101 aacttatatt ggaaaaatta taggttattc aataaactta cggaatgatt atctgattct
20161 catctttgat atgtgcttca agtgcacctg aggtaattaa catatcaaag ttatccacat
20221 aagttctcgg gtttgtggca tagcaaacta atccaacttg aatcagtgtt ttatctgtga
20281 tctcagcagt attcagagtt gaagcgggcg atggaagttt gaatgcccat tcttcacagt
20341 tttgagtttt tcctacaata tttgatgcat catcgataac gattaccatt ccggttccgt
20401 cgacgctatt ctaaaaattt gattgacatt agtgtaaact gtaacttttt gattaccgag
20461 tagtcataag gtaagttgcc agttgctata gctctagctg ctagcgtgtt ttccagggta
20521 tctagtgtag atgcaagttg gttggctaga tttttggcct gaatagaata tgaataattc
20581 caaactcaaa aagttttaaa aactcacgat gttcttctgg aacatttttg tgacgtaagc
20641 agcccattct tctgacgtca tttcctccac gtacacaata ttgtctggat cacttggtag
```

```
20701 cacgttgtac aaggaatcat agttatctgt tgcatatttc aaattggcag ctagatcaga
20761 agaaagagga ttgtcgagag caatcttcaa cgctgatgtt aaagatcccg caattgaaag
20821 gagagagttg gatgtctgaa aattattatt atgacatcta ccaaagttta gtgtatgaat
20881 acatcattaa tctctgcatc tgtcatagtc attccattat ttgtaagaaa atcttgagta
20941 ttgctaagaa tcgtttcaat ttgttgctgg gattcttgat tcatcaaact ttgcggcaca
21001 atatctggat atttaaaatg atttgtatgc atttgtgtat ttatttttt gagttaccaa
21061 ttttagttcc cgaaacatcg ccttccgtcg aaacttgtcc attctgaatt acatatccat
21121 tcgttccatt tctaataatc aaccctccat cgattctcat tttctgtgtg tcagagaatt
21181 ccattaaagt tctcaaaatt aaagttccta tacaaaatat ccattcgaga ctatacttac
21241 accgtatgag tttgagaacc agatgtgtaa gttccggctg ttatctgaat accgtaacct
21301 ccaagcgcca aagaaacaat attgtaggtg ggagaactga tcaccagagt tgtcacagag
21361 tttgacaaat aaagggcggt ggagtctacg aaaaatgagt agccgctgac atcgatggat
21421 gacgctttgg agaagaatag ctgcaagaaa agttattttg atattaacaa ctcatcagca
21481 aaagtcttac agttcccgaa acggtgacaa gtgtttgttc cttaatcaat gattgcaaat
21541 catctttggt gtacgaagcc gtcggtgaaa gagtagatat tgagacagtt tgagataaag
21601 cagagacagc tggaattcca atgtcctgcg gagacagcac cattcgcatt gaataacttc
21661 ccgcgtttga gaacacaagt ggagaagtag tttgattgaa taaagcaagg ttgacgtctg
21721 aaatttttag cgtcataacc agaccactcc cattgcatac ttactctcaa taactatcgg
21781 catctgaatc aacttcttaa ccgtgctcgc tgaggatcca tctgatgcca caaccgtgaa
21841 gctgtcagca ttgtatgaga aaatggcatt atctgtgtct acttcaacaa actttcctgt
21901 tccattcgtg caagttattg tgtaagtaac tccaccatat gatgcagtta ctactagtcc
21961 tctagataca atattttgag tagaatgcag ttttatcatt gttccagatt caatctgaat
22021 aaaaattgaa aaatttcatg tgctctacga tttataaatt taccaataat atgtattgaa
22081 cttctgagac tgggatattg aacgaaaatg aagtgttctt ctgacttgtg gatcctactg
22141 ttgaattgtc ataagtgaca ttccaagcag ttacatacat atcattataa ctatattccc
22201 ctgattgaac atctccaact ccactcattg tagccattat atttccagaa accagtgatc
22261 gtttgtcatc tattttatcc tgctcaactt gcacagtcct tccatttgtt gcgaacattc
22321 cttggattcc gatggcagct gctagcatag tgtccgcctg aacagtttca cataaactac
22381 aatgttctat attcaaaaag tcttacagta acggtatctc catcaagctg tttataagat
22441 gcccgggtat ctcctgtaag gtatattgta gatccgtaaa tgctgagctg taagttgaaa
22501 acaattaact ctcccaacca tcattttctt accgtacacc taggcgatac caatgtatat
22561 cccgatgcaa taacatatcc aaaaataacc gcgtaagttc catcttttga ttttgtactt
22621 gatactccca aggtatagac tgtacttcct ttgagagcaa gatcgagaga agacagtacg
22681 gagttcaagg attgtgcgga agtcatattg acatttgcta gtttagtgat aacttttgcc
22741 atttcgtcgg ccaattccga atttgttgtt gcaatattgt cttgcaatgt tttcaaaaca
22801 tcaacacttg acatatttcc gactccaggg attttgaggg tatttgagag caaactttga
22861 gcaacttcca ctagatctgc ggcaggtaga gatgagattt gattgagaag agagctgctt
22921 gtgtttagag agttgttgga tgcagatcca tccattatcc cagccagttg gttcattaca
22981 tcagcttttt gagcatctat gatcgcttgt tcagctgcag aaattggaga aactgttgca
23041 agagagctgc gagttttagt agttcttgta gatggttgcg cggtagcaga gaatgcacca
23101 tttgcaccag aggaatcgga agatccagac gtatcggagc cagatgagct cttggttgaa
23161 acaccagaag atccatttga atctgatcct gagccagatg tactaccacc gtctcctaaa
23221 tgggatcctg gtgtggtagc tgttccagat cctgtaccat ctccattcaa tgccgttgtt
23281 tttccagagt ttaccccgtc cgaacccgtc cctgaagacc cccctgaccc acttccagaa
23341 gcggtcgttc ctgatccacc agcccccgat cccgttgatg attgtccact tccagatcca
23401 gaagtggttg atctgactgc atcacccgtg ctaagagttg tcgcagatcc tcctgaacct
23461 gttccaccag ttccccccagt agctccagtt ccaccggttt tgccaccggc atcatccgac
23521 gagctgacag tggttggtgg ggtttctaaa aattgaattt tatgaaaaaa aaacagtaat
23581 gcgcttacca gtagttgtag ttggaagaac tacattcata gtaaagatgt gactggcaga
23641 ttctccagat gcacgattgg taacattaat taagaattca taagttccag ttgcaggtac
23701 aaagctggtc attgggttga aagatacgga ggcactatat gcaccatttt ttccaactgt
23761 aatatagtac ataaatgaaa attgataacg ttgctaacta gggagtgctc tttgtactcc
23821 atggaaatat gagtcggaaa actacttttc gggtagttta tgtcattttc tacacgattc
23881 tgaaagaaaa tcctgccggt tttgggtttt agtgtgaaaa gtttgcgttt gaaaatacca
23941 ccctaaattc agttgattta acactacgcg acccatattt catgtgcaac gggaaagcca
24001 agtacactga aaactcactt tcaaattttc aaagcaaagt cataatttcg gtggtccagt
24061 ggataacggc gggagcggcg ccagttttca gtgtacttgg ctttcccgtt gcacatgaaa
24121 tatgggtcgc gtagtgttaa atcaactgaa tttagggtgg tattttcaaa cgcaaacttt
24181 tcacactaaa acccaaaacc ggcaggattt tctttcagaa tcgtgtagaa aatgatatca
24241 actaccggaa aagtagtttt ccgactcata tttccatgga gtacaaaaag cactccctag
24301 taggcaaaat ctcacactct gtcaagcaat tgctttcctt cagtaaaaca aatggctgag
24361 aagaatcgtt tcgacattga caggtcatag cagtcttaaa atattaaggt ttttttaag
24421 taagattgat ttgaatatct taccgttaaa gctccgggct ctttgtttgg aattggtgta
24481 atataaaatg gattttcaga gtaatacact gtctcgttcc atgtcaaatt ttccaataca
```

```
24541 aagtcgtaag gggtttctgt acttgcgtct ggatccacag ttgttgttct catgctatca
24601 gatgcacttg atgaatcgga tggtgtttga gataaaccag atgaatctga agtggatgga
24661 gttgagttag atgagtctat ggtggtggaa tctgaagttg tgccagaatc cgatgttgat
24721 gtagaactgt cttgtgaagc atcagtcgtg ctagcttcca aagtcgacgt agattcaatt
24781 cctgaagttg tggaaatggc tgaactttcg gaagaagatc cagttgaagt tgtactggta
24841 acttcggatg tacttgttga atccgcaaca acattcaatg tgaaaatgtg gctgaccact
24901 tgcattgtcg tcaaatccgt catgttgatt cgaaactcat aggtgccaat gccaacaaga
24961 aatgtttcaa ttggttgaat tggaatatta gaagaataag ttgcgtttag gaccgtgttt
25021 gctggaaatt cgctttaatt caataatttc aaaaagtttg ttaatcctac agtagtttaa
25081 gcaagtggat tccttaatta taagaaaagg ctcagtagac acatttctgc attcaaatgt
25141 ttggcttctc taaaatcatt cgtttcattt ggctcaacga tttattaaac ccgcctcagt
25201 aggagtaatg gcattagttg gtaaaggtac aatgttgatg ctgtcttcat tgtgacgtgt
25261 ctcgttccat gacaatccac tgtccaagat gaaatcgaac tgatcgactg acaaagtgga
25321 agttgaatca gcagtggtag aactcggact ggaagaagtt gtggatgtgt ccgagatggt
25381 agttgtactg gaatcagtag tactttcttc ggaagttgtt gtggattctt gtaaagtagt
25441 tgtgctccca gccgacgttg tcgtagaatc gcttgaacgt gtggatgacg gctctgtgac
25501 tgtggatgtt gataatgtgg aagatggagt tgatggtgta gatgacgtag agcttgctac
25561 agcagatgta gaagattccg actctatggt ggtggaagaa tattcctgaa tataaacgtt
25621 cgcatacgtg tagtaaactt ttttatcgtc ggttgtcata gttgctctga aggtgtagtt
25681 tccaggacca acgaatgtgc tagcagggta cgtccctccg agacgtggca ttgatacact
25741 ttctgaatat attgaaaaaa tatgtgtaaa aaatctaaat aactatcgcc cgaaaaaggt
25801 ttgctttttt tccgatttga agtttttata gaaacgtttt cagaattaaa gattttgcct
25861 gtctctaatt tataataagt ctttataaac aattactcgt gaaacatgct ccgtctttag
25921 tggttgaaac ataattagaa gatgtagggc ttgtacattc gatggatgtt tgatactgaa
25981 atacagtgtt acatttgaat aatgcagtct tcaatattgt acttactcca atgattccga
26041 ggccggaatt aagcgttagg ttcacacttg tggaatcata gaacgttgta gttgcctttt
26101 ctacaaaata gaagtctgga ttagttccgt ccgagctagt agttgtctca gattttgttg
26161 ttgttgaact ttgctgagta gacgtggatg attgagtaga agaagcggtg cttgacacag
26221 acgaagaagc cgttgaactt ggagtggaag aagaactcga tggcccagta gttgatgttg
26281 aaggagcagt tgtgctggtt gttactgtag acgaaggaga tgtcgatgtg gactcagtgc
26341 ttgttggggt cgttacagta gtcgaggagc ttgaactaga tgtcaccgta gaagtcacag
26401 gggatgttga cggggaagta gttacagtac tcgtcgatgg ttcggttgtt gacgttgaag
26461 cagtcgaggt ggtcaaagta gtggttggtt cagttgttgt aacagtagaa gatgtagatg
26521 taacttctgt tgtggttgtg gaagtagatg gttcttcggt agtagtggat gtcaacatag
26581 tggtggtgaa agtggtagac gtagtggtct cgtcaaggta ggagcaaatc gcattatccg
26641 ggagagacga caaagttgct gaaaattttc gttaaggatt ttctggataa ctaacaatgc
26701 acaacaaggt gatcggtaat agtgactgct ttgttttacc ctgagcaaac tgtaattgta
26761 taaaatctga aatattggca atacaaacgg gtttgaagaa aattattaac aattttattc
26821 ctgcctctca atcataacag caaattctgg tttgcttgta attattattg tgcgtccgaa
26881 actcacatgt gatttcgggt gttgtagtgg ttggaatact tgtactcagt gtggtggagc
26941 tcggcgagct tgtgattgtg ctagaactct gctgagttgt gctagttgat gatgtcgacg
27001 tggatgctgt ggaagtgaac gttgttgacg tggattcgat ggtggtggat gttgatggag
27061 ttgatgtgct tgtgctcatt gcggtagtca ccgtacttgt acttgttggg acggttgttg
27121 tagatgtcac ggtactagtc acggttgtgg tagttggagt tgtagtcgag gttgaagttg
27181 actcaatagt gtagtcgcaa gtattatcac cctggaataa aatgaaagta aacactatct
27241 gagaaatcgt actcacagcg tctcgtttca ttcttctcaa agtaggtgat ccagaagtcc
27301 tcatgctaaa ctgttttgcc ctgacaccct taagtacctg cccatcataa tacactcctt
27361 gactatcact gatagctgtg ctcttttcag aacgatctga aatactgttt agccaatgtt
27421 catgagcaat taagaactga caaggtcgct tgcacattct tctcgcatac tcttcgttga
27481 tctctccgct ctcacacttc tctcggtagc ccagcaacgc catctcgttt ccaccgactt
27541 ggagccacca tagggagcca tcacatctgt cgataccgtc atctgagaaa gagtttctat
27601 taaaatgtta gaaacacata gcactacata tgcaaataac gtttcaccag attcagaatg
27661 cgcaattcat gcctatctca tagcctacct atgtgtctac ctgagtatct acttgagtac
27721 cttgcaaaga agattaatcg gcacaaacca agtcaagact ttgttggcat aggtcttcca
27781 ggtgagtaac gccgacatta tacataggta cgcacaaaac cttccccaaa taataatcct
27841 taccataaca aacttcatat ttcgcctcca cagcaatact gatctcatcg tcatcattca
27901 cttcattcaa agtaatccaa gttgagttca aaaagagtcc gacaagcctg gtctctgttt
27961 ggatgcagtt gtgaatctga a
//
```

sparc-sun-solaris2.8 Oct 1 2001 12:59:49